| | Type | Ref # | Hits | Search Text |
|---|---|---|---|---|
| 1 | BRS | S1 | 199 | treatment and cerebrovascular adj ischemia |
| 2 | BRS | S2 | 3 | S1 and peptide adj treatment |
| 3 | BRS | S3 | 0 | S1 and peptide near for near treatment |
| 4 | BRS | S4 | 85 | S1 and peptide |
| 5 | BRS | S5 | 2 | S4 and cerebral adj embolism |
| 6 | BRS | S6 | 0 | S4 and erectile adj dysfuntion |
| 7 | BRS | S8 | 0 | S4 and improve adj blood adj flow |
| 8 | BRS | S7 | 4 | S4 and hair adj loss |
| 9 | BRS | S9 | 6 | S4 and VIP |
| 10 | BRS | S10 | 5 | S4 and PACAP |
| 11 | IS&R | S11 | 1 | ("5208320").PN. |
| 12 | BRS | S12 | 0 | h s d a i f t d s y s r y r r q l a v r r y l a a v l g r r |
| 13 | BRS | S13 | 0 | (PACAP adj (analogs or analogues)) and ischemic adj cerebrovascular adj disorder |
| 14 | BRS | S14 | 27 | (PACAP adj (analogs or analogues)) |
| 15 | IS&R | S15 | 1 | ("4939224").PN. |
| 16 | BRS | S16 | 231 | (vasoactive adj intestinal adj peptide or VIP) adj (analog or analogue) |
| 17 | BRS | S17 | 9 | (vasoactive adj intestinal adj peptide or VIP) adj (analog or analogue) and cerebrovascular adj disease |
| 18 | IS&R | S18 | 1 | ("4605641").PN. |
| 19 | IS&R | S19 | 2 | (("3880826") or ("4016258")).PN. |
| 20 | IS&R | S20 | 1 | ("20060276384").PN. |
| 21 | IS&R | S21 | 1 | ("6680295").PN. |
| 22 | IS&R | S22 | 1 | ("6242563").PN. |
| 23 | BRS | S23 | 0 | h s d a i f t d s y s r y r r q l a v r r y l a a v l g r r |
| 24 | IS&R | S24 | 1 | ("2004224775").PN. |
| 25 | IS&R | S25 | 1 | ("2004315436").PN. |
| 26 | IS&R | S26 | 1 | ("20040128581").PN. |
| 27 | IS&R | S27 | 0 | ("200400128581").PN. |
| 28 | IS&R | S28 | 0 | ("20040330464").PN. |
| 29 | IS&R | S29 | 1 | ("2004315436").PN. |
| 30 | IS&R | S30 | 1 | ("20040109827").PN. |
| 31 | IS&R | S31 | 2 | (("6372628") or ("6091081")).PN. |
| 32 | IS&R | S32 | 1 | ("20040132648").PN. |

=> s treat (w) ischemic (w) cerebrovascular
L7 12 TREAT (W) ISCHEMIC (W) CEREBROVASCULAR

=> s (treat or prevent) (w) ischemic (w) cerebrovascular
L8 15 (TREAT OR PREVENT) (W) ISCHEMIC (W) CEREBROVASCULAR

=> d l8 1-15 abs

L8 ANSWER 1 OF 15 MEDLINE on STN
AB Breviscapine, a well-known bioactive flavonoid ingredient extracted from the traditional Chinese medicine, has been extensively used in clinic to ***treat ischemic cerebrovascular*** and cardiovascular diseases in China. In order to prolong the duration of the drug in the circulation, reduce the frequency of injection administration and subsequently afford patient compliance, multivesicular liposome (MVL, namely DepoFoam) was utilized as a sustained-delivery system for breviscapine. In vitro release and in vivo pharmacokinetics of MVLs containing breviscapine (bre-MVLs) following intramuscular injection to rats were investigated compared with those of traditional liposomes containing breviscapine (bre-TLs). The drug durations both in vitro and in vivo were significantly prolonged for the bre-MVL, and that the drug release in vitro and the absorption in vivo showed a good linear correlation (R=0.9834), which provided an evidence for the suitability to select human plasma as the medium of drug release from MVLs in vitro. Drug release from bre-MVLs (triolein/tricaprylin, 10/0) in vitro extended a long period of 5-6 days, while the bre-TLs released 80% within only 4h. The mean residence time (MRT) obtained from the pharmacokinetics study of bre-MVL was about 16.6- and 5.04-fold longer than those of breviscapine solution (BS) and bre-TL, respectively. A duration in vivo for a period of 4-5 days was fulfilled for bre-MVL. In conclusion, MVL can be successfully used as a sustained delivery system of breviscapine.

L8 ANSWER 2 OF 15 MEDLINE on STN
AB Measurements of CBF and CMR in human ischemia and infarction have provided valuable insight into the pathophysiology of stroke and important guidance to the development of therapeutic strategies. Further research combing therapeutic manipulation with CBF and CMR will be important for developing optimal methods to ***treat ischemic cerebrovascular*** disease. At this time, no value has been demonstrated for these techniques in individual patient care decisions. Although now widely available, CBF and CMR measurements should still be considered clinical research tools until they can be shown to provide benefit in reducing morbidity and mortality or reducing medical expenses in clinical practice.

L8 ANSWER 3 OF 15 MEDLINE on STN
AB This notice announces the withdrawal of Medicare coverage of extracranial-intracranial (EC-IC) arterial bypass surgery when used to treat or ***prevent ischemic cerebrovascular*** disease of the carotid or middle cerebral arteries. Available evidence does not show that this surgery is effective.

L8 ANSWER 4 OF 15 MEDLINE on STN
AB This notice announces the Medicare program's intent to withdraw Medicare coverage of extracranial-intracranial (EC-IC) arterial bypass surgery when used to treat or ***prevent ischemic cerebrovascular*** disease of the carotid or middle cerebral arteries. Available evidence does not show that this surgery is effective.

L8 ANSWER 5 OF 15 MEDLINE on STN
AB The therapeutic effect and laboratory finding in the treatment of 288 cases of ischemic cerebrovascular disease with PSS were analysed. Positive therapeutic response to PSS in this series of cases was obtained

in 92.0% and 62.2% of the treated cases showed excellent results. Effects in the treated patients were better than in the controls. The laboratory findings showed that PSS had obvious anticoagulant effect and decreased blood viscosity and serum contents of lipids. The results of animal experiments showed that PSS had the action of blood dilution, lowering blood viscosity and ameliorating hypercoagulation. PSS was considered to be a prospective, useful drug to prevent and ***treat ischemic cerebrovascular*** disease.

L8 ANSWER 6 OF 15 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AB Breviscapine, a well-known bioactive flavonoid ingredient extracted from the traditional Chinese medicine, has been extensively used in clinic to ***treat ischemic cerebrovascular*** and cardiovascular diseases in China. In order to prolong the duration of the drug in the circulation, reduce the frequency of injection administration and subsequently afford patient compliance, multivesicular liposome (MVL, namely DepoFoam) was utilized as a sustained-delivery system for breviscapine. In vitro release and in vivo pharmacokinetics of MVLs containing breviscapine (bre-MVLs) following intramuscular injection to rats were investigated compared with those of traditional liposomes containing breviscapine (bre-TLs). The drug durations both in vitro and in vivo were significantly prolonged for the bre-MVL, and that the drug release in vitro and the absorption in vivo showed a good linear correlation (R = 0.9834), which provided an evidence for the suitability to select human plasma as the medium of drug release from MVLs in vitro. Drug release from bre-MVLs (triolein/tricaprylin, 10/0) in vitro extended a long period of 5-6 days, while the bre-TLs released 80% within only 4 h. The mean residence time (MRT) obtained from the pharmacokinetics study of bre-MVL was about 16.6- and 5.04-fold longer than those of breviscapine solution (BS) and bre-TL, respectively. A duration in vivo for a period of 4-5 days was fulfilled for bre-MVL. In conclusion, MVL can be successfully used as a sustained delivery system of breviscapine. (C) 2005 Elsevier B.V. All rights reserved.

L8 ANSWER 7 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
AB An invention involving the preparation of compounded medical formulation of ligustrazine phosphate and xylitol. The medical preparation may ***treat ischemic cerebrovascular*** disease, or diabetes accompanied by cerebrovascular diabetes. The medical preparation contains ligustrazine phosphate, xylitol, adjuvant, and additive. medical preparation may be injections, tablets, capsules, granules pills, oral solns., sprays, soft capsules, dripping pills, sustained release or fast release or controlled release preparation

L8 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
AB The title drop pill is prepared from Salvia miltiorrhiza, Ligusticum chuanxiong, Radix Puerariae (Pueraria lobata and/or Pueraria thomsonii) and appropriate amount of adjuvant. It has effects in promoting blood circulation and removing blood stasis; and can be used to ***treat ischemic cerebrovascular***; ischemic cardiovascular, arteriosclerosis, cerebral thrombosis, cerebral ischemia, coronary heart disease, and angina pectoris, with the advantages of convenient administration, rapid action, remarkable curative effect, and no side effects. It offers a new dosage form for the choice of doctors and patients.

L8 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
AB Breviscapine, a well-known bioactive flavonoid ingredient extracted from the traditional Chinese medicine, was extensively used in clinic to ***treat ischemic cerebrovascular*** and cardiovascular diseases in China. In order to prolong the duration of the drug in the circulation, reduce the frequency of injection administration and subsequently afford patient compliance, multivesicular liposome (MVL, namely DepoFoam) was utilized as a sustained-delivery system for

breviscapine. In vitro release and in vivo pharmacokinetics of MVLs containing breviscapine (bre-MVLs) following i.m. injection to rats were investigated compared with those of traditional liposomes containing breviscapine (bre-TLs). The drug durations both in vitro and in vivo were significantly prolonged for the bre-MVL, and that the drug release in vitro and the absorption in vivo showed a good linear correlation (R = 0.9834), which provided an evidence for the suitability to select human plasma as the medium of drug release from MVLs in vitro. Drug release from bre-MVLs (triolein/tricaprylin, 10/0) in vitro extended a long period of 5-6 days, while the bre-TLs released 80% within only 4 h. The mean residence time (MRT) obtained from the pharmacokinetics study of bre-MVL was about 16.6- and 5.04-fold longer than those of breviscapine solution (BS) and bre-TL, resp. A duration in vivo for a period of 4-5 days was fulfilled for bre-MVL. In conclusion, MVL can be successfully used as a sustained delivery system of breviscapine.

L8 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
AB A review on clin. trials of antithrombotic therapy for prevention of ischemic cerebrovascular diseases including stroke with anticoagulants and antiplatelet agents such as aspirin, thienopyridine, cilostazol, GP IIb/IIIa inhibitors, and warfarin. The guideline of antithrombotic therapy for prevention of stroke is also discussed.

L8 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
AB The medical composition is composed of 5-25% scutellarin and 45-95% a mixture of caffeoylquinic acid and dicaffeoylquinic acid, and prepared by extracting Erigeron breviscapus with 80% alc. thrice, concentrating; dissolving the extract in water, adjusting pH to about 7, filtering, adjusting pH to 1-3, extracting with 1-butanol 4 times, concentrating, drying in vacuum to obtain the medical composition in a free base form; or neutralizing with 10% NaOH to pH 7-8, and spray drying to obtain the medical composition in a Na salt form. The medical prepns. (such as tablet, capsule, pill, granule, oral solution, etc) are prepared and used to prevent and ***treat ischemic cerebrovascular*** and cardiovascular diseases, senile dementia, hypertriglyceridemia, and viral hepatitis.

L8 ANSWER 12 OF 15 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
AB Breviscapine, a well-known bioactive flavonoid ingredient extracted from the traditional Chinese medicine, has been extensively used in clinic to ***treat ischemic cerebrovascular*** and cardiovascular diseases in China. In order to prolong the duration of the drug in the circulation, reduce the frequency of injection administration and subsequently afford patient compliance, multivesicular liposome (MVL, namely DepoFoam) was utilized as a sustained-delivery system for breviscapine. In vitro release and in vivo pharmacokinetics of MVLs containing breviscapine (bre-MVLs) following intramuscular injection to rats were investigated compared with those of traditional liposomes containing breviscapine (bre-TLs). The drug durations both in vitro and in vivo were significantly prolonged for the bre-MVL, and that the drug release in vitro and the absorption in vivo showed a good linear correlation (R = 0.9834), which provided an evidence for the suitability to select human plasma as the medium of drug release from MVLs in vitro. Drug release from bre-MVLs (triolein/tricaprylin, 10/0) in vitro extended a long period of 5-6 days, while the bre-TLs released 80% within only 4 h. The mean residence time (MRT) obtained from the pharmacokinetics study of bre-MVL was about 16.6- and 5.04-fold longer than those of breviscapine solution (BS) and bre-TL, respectively. A duration in vivo for a period of 4-5 days was fulfilled for bre-MVL. In conclusion, MVL can be successfully used as a sustained delivery system of breviscapine.

L8 ANSWER 13 OF 15 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

AB Background: Batroxobin, one of the ideal and well-received medicines to ***treat ischemic cerebrovascular*** diseases at present, is widely used in clinic. Therefore, it is necessary to further understand its protective function in cerebral ischemic reperfusion injury. Objective: To explore the effects of batroxobin on platelet-activating factor(PAF) and expression of platelet-activating factor receptor mRNA (PAF-R mRNA) in rats after focal cerebral ischemic reperfusion. Design: A completely randomized group-dividing design. Setting and participants: The experiment was completed in Scientific Research Center of the Second Hospital affiliated to Harbin Medical University from March to December in 2004. Forty healthy male Wistar rats, weighting 200-250 g, were chosen. They were divided into 5 groups randomly, 8 in each group. Group I was sham-operation group. Group II was normal saline group. Group II a was 6 hours ischemia and 6 hours reperfusion group while group II b was 6 hours ischemia group. Group III was batroxobin group. Group III a was 6 hours ischemia and 6 hours reperfusion group while group III b was 6 hours ischemia group. Methods: Thread-tying method was used to establish the model of middle cerebral artery occlusion (MCAO) and recanalization. RT-PCR technique was applied to detect the expression of PAF receptor gene in ischemic semidark band cortex after MCAO and recanalization. At the same time ELISA method was used to determine the corresponding PAF values in plasm. Main outcome measures: PAF-mRNA expression in ischemic semidark band cortex and PAF levels in plasm at different time points. Results: PAF levels in reperfusion group and ischemia group of normal saline group increased obviously, (1 480 ± 249) ng/L in group II a and (1 052 ± 199) ng/L in group II b, respectively. By contrast, expression of PAF-R mRNA decreased, (0.44 ± 0.06) in group II a and (0.48 ± 0.05) in group II b, respectively. Compared with corresponding sham-operation group, there was significant difference($P < 0.01$). In batroxobin group, PAF levels in reperfusion group (848 ± 80) pg/mL and ischemia group (743 ± 105) ng/L decreased, but expression of PAF-R mRNA increased, (0.63 ± 0.08) in group III a and (0.67 ± 0.06) in group III b. Compared with normal saline group, there was significant difference ($P < 0.01$). Conclusion: Batroxobin can decrease PAF level in plasm after cerebral ischemic reperfusion and may have some effects on PAF-R m-RNA expression in semidark band cortex after cerebral ischemic reperfusion, which provides experimental data for prophylactic intervention.

L8 ANSWER 14 OF 15 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

AB Aim: To observe the changes of the somatosensory evoked potentials(SEP) before and after transplanting mesenchymal stem cells(MSCs) into the infarcted rats, in order to explore the effects of MSCs transplantation on the objective examining indexes of neural function. Methods: Rat models of middle cerebral artery occlusion(MCAO) were established, then the MSCs isolated and cultured in vitro were injected into the infarcted region of the rats, and the SEP was examined before(1week after MCAO), 2 and 4 weeks after transplantation. Results: All the indexes of SEP in the transplantation treated group were improved obviously than those before transplantation. Four weeks after transplantation, the peak value of P1-N1 were(4.26 ± 1.53) μV, the latencies of P1 and N1 were(14.07 ± 3.01) ms and(15.62 ± 2.93) ms, respectively; while before transplantation, the peak value of P1-N1 was (2.34 ± 1.62) μV, the latencies of P1 and N1 were(17.33 ± 2.35) ms an (19.23 ± 3.16) ms, respectively; and there were obvious improvements compared with the control group, and the differences were significant ($P < 0.05$). Conclusion: Animal experiment shows that the MSCs transplantation promotes the recovery of neural function to a certain degree, and provides a new method to ***treat ischemic cerebrovascular*** diseases.

L8 ANSWER 15 OF 15 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

AB Measurements of CBF and CMR in human ischemia and infarction have provided valuable insight into the pathophysiology of stroke and important guidance to the development of therapeutic strategies. Further research combining therapeutic manipulation with CBF and CMR will be important for developing optimal methods to ***treat ischemic cerebrovascular*** disease. At this time, no value has been demonstrated for these techniques in individual patient care decisions. Although now widely available, CBF and CMR measurements should still be considered clinical research tools until they can be shown to provide benefit in reducing morbidity and mortality or reducing medical expenses in clinical practice.

=> s vip or pacap and (treat or prevent)(w)relaxing (w) bronchial(w) smooth (w) muscle
L9 37379 VIP OR PACAP AND (TREAT OR PREVENT)(W) RELAXING (W) BRONCHIAL(W) SMOOTH (W) MUSCLE

=> s (vip or pacap or pharmaceutical (w) composition) and (treat or prevent)(w)relaxing (w) bronchial(w) smooth (w) muscle
L10 0 (VIP OR PACAP OR PHARMACEUTICAL (W) COMPOSITION) AND (TREAT OR PREVENT)(W) RELAXING (W) BRONCHIAL(W) SMOOTH (W) MUSCLE

=> s (vip or pacap or (pharmaceutical (w) composition)) and (treat or prevent)(w)relaxing (w) bronchial(w) smooth (w) muscle
L11 0 (VIP OR PACAP OR (PHARMACEUTICAL (W) COMPOSITION)) AND (TREAT OR PREVENT)(W) RELAXING (W) BRONCHIAL(W) SMOOTH (W) MUSCLE

=> s vip or pacap and (treat or prevent)(w)ischemic (w) cerebrovascular(w) disorder
L12 37379 VIP OR PACAP AND (TREAT OR PREVENT)(W) ISCHEMIC (W) CEREBROVASCULAR(W) DISORDER

=> s vip or pacap and (treat or prevent)(w)disorder
L13 37380 VIP OR PACAP AND (TREAT OR PREVENT)(W) DISORDER

=> s vip and treat(w) disorder
L14 0 VIP AND TREAT(W) DISORDER

=> s vip (w) treat(w) disorder
L15 0 VIP (W) TREAT(W) DISORDER

=> d l9 1 abs

L9 ANSWER 1 OF 37379 MEDLINE on STN

AB BACKGROUND: Morita therapy was founded in 1919 by Shoma Morita (1874-1938). The therapy involves a behavioural structured programme to encourage an outward perspective on life and hence an increased social functioning. OBJECTIVES: To evaluate the effects of Morita therapy for schizophrenia and schizophrenia-like psychoses. SEARCH STRATEGY: We searched the Cochrane Schizophrenia Groups Trials Register, the Chongqing ***VIP*** Database, the Wanfang Database (August 2006), all relevant references and contacted the first author of each included study. SELECTION CRITERIA: We included all randomised clinical trials comparing Morita therapy with any other treatment. DATA COLLECTION AND ANALYSIS: We reliably selected studies and extracted data. For homogenous dichotomous data we calculated random effects, relative risk (RR), 95% confidence intervals (CI) and, where appropriate, numbers needed to treat (NNT) on an intention-to-treat basis. For continuous data, we calculated weighted mean differences (WMD). MAIN RESULTS: We found 11 small, studies of medium-poor quality (total n=1041). The standard care versus Morita therapy comparison (total n=679 people) had very low attrition (<2%, 9

RCTs, RR 1.02 CI 0.3 to 3.1). Mental state did tend to improve with Morita therapy (n=76, 1 RCT, RR no >25-30% decline in BPRS RR 0.36 CI 0.1 to 0.9, NNT 5 CI 4 to 25). For negative symptoms data were inconsistent, with data from three trials favouring Morita therapy (n=243, RR -10.87 CI -20.5 to -1.2), but heterogeneity was considerable (I(2) =92%). Morita therapy plus standard treatment did significantly improve the ability of daily living compared with standard treatment alone (n=104, 1 RCT, WMD -4.1 CI -7.7 to -0.6). Compared with a rehabilitation programme Morita therapy did not promote attrition (n=302, 2 RCTs, RR 1.00 CI 0.5 to 2.1). In two very similar studies Morita therapy showed better effect on mental state with lower BPRS score (n=278, 2 RCTs, WMD -6.95 CI 9.3 to 4.6, I(2) =0%) insight (n=278, 2 RCTs, WMD -1.11 CI -1.3 to -0.9, I(2) = 0%) and social functioning (n=278, WMD average IPROS score -18.14 CI -21.3 to -15.0, I(2) =0%). AUTHORS' CONCLUSIONS: Currently trial based data on Morita therapy is inconclusive. Morita therapy for schizophrenia remains an experimental intervention, new trials are justified and specific outlines for design of future studies are outlined in additional tables.

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=> s l9 367 abs
MISSING OPERATOR L9 367
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> d l9 367 abs

L9    ANSWER 367 OF 37379      MEDLINE on STN
AB    Cancer patients undergoing radiation treatment are exposed to high doses
      to the target (tumour), intermediate doses to adjacent tissues and low
      doses from scattered radiation to all parts of the body. In the case of
      proton therapy, secondary neutrons generated in the accelerator head and
      inside the patient reach many areas in the patient body. Due to the
      improved efficacy of management of cancer patients, the number of long
      term survivors post-radiation treatment is increasing substantially. This
      results in concern about the risk of radiation-induced cancer appearing at
      late post-treatment times. This paper presents a case study to determine
      the effective dose from secondary neutrons in patients undergoing proton
      treatment. A whole-body patient model, VIP-Man, was employed as
      the patient model. The geometry dataset generated from studies made on
      VIP-Man was implemented into the GEANT4 Monte Carlo code. Two
      proton treatment plans for tumours in the lung and paranasal sinus were
      simulated. The organ doses and ICRP-60 radiation and tissue weighting
      factors were used to calculate the effective dose. Results show whole
      body effective doses for the two proton plans of 0.162 Sv and 0.0266 Sv,
      respectively, to which the major contributor is due to neutrons from the
      proton treatment nozzle. There is a substantial difference among organs
      depending on the treatment site.


=> s vasoactive(w
MISSING OPERATOR 'VASOACTIVE(W'
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s vasoactive(w)intestinal(w) peptide and treat(w) disorder
L16           0 VASOACTIVE(W) INTESTINAL(W) PEPTIDE AND TREAT(W) DISORDER

=> s (vasoactive(w)intestinal(w) peptide) and treat(w) disorder
L17           0 (VASOACTIVE(W) INTESTINAL(W) PEPTIDE) AND TREAT(W) DISORDER

=> s (pituitary (w)adenylate(w)cyclase(w)activating(w)polypeptide)
L18        7888 (PITUITARY (W) ADENYLATE(W) CYCLASE(W) ACTIVATING(W) POLYPEPTIDE
                )
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=> s (vasoactive(w)intestinal(w)pepetide)
L19           0 (VASOACTIVE(W) INTESTINAL(W) PEPETIDE)

=> s (vasoactive(w)intestinal(w)peptide)
L20       30706 (VASOACTIVE(W) INTESTINAL(W) PEPTIDE)

=> s l20 and cerebrovascular
L21         158 L20 AND CEREBROVASCULAR

=> s l20 and broncial(w)smooth(w)muscle
L22           0 L20 AND BRONCIAL(W) SMOOTH(W) MUSCLE

=> s l18 and cerebrovascular
L23          45 L18 AND CEREBROVASCULAR

=> d l23 1-10 abs

L23  ANSWER 1 OF 45      MEDLINE on STN
AB   BACKGROUND: Vasoactive intestinal peptide (VIP), and pituitary adenylate
     cyclase-activating peptide (PACAP), are members of a VIP/secretin/glucagon
     family.  These peptides were demonstrated to possess the neuroprotective
     properties.  However, these peptides are not suited to be developed as a
     medicine for brain ischemia because of their susceptibilities to
     endopeptidases.  METHODS: We examined the effects of IK 312548 (IK), VIP
     derivative, and Ac-PACAP, PACAP derivative, on the 10 min two-vessel
     occlusion (2 VO) model in C 57 BL/6 N mice lacking a part of the posterior
     communicating artery, and the 30 min middle cerebral artery occlusion
     (MCAO) model in ICR mice.  A 10 ml x kg(-1) dose of each derivative (final
     concentration; 1 fmol x kg(-1) and 100 pmol x kg(-1)) was injected
     intraperitoneally (i.p.) to each animal just after the preparation of
     brain ischemia.  RESULTS: In 2 VO experiments, the number of neuronal
     cells in hippocampus was significantly reduced.  However IK and Ac-PACAP
     treatments inhibited such reductions of neuronal cells in a dose-dependent
     manner.  Particularly, between 1 pmol x kg(-1) and 100 pmol x kg(-) IK,
     and also between 10 fmol x kg(-1) and 1 pmol x kg(-1) Ac-PACAP
     significantly protected neuronal cell loss.  In MCAO experiments, more
     than 60% of hemisphere was damaged.  By treatment of IK (1-100 pmol x
     kg(-1)) and Ac-PACAP (1 fmol-1 pmol x kg(-1)), the range of brain damage
     decreased in a dose-dependent manner.  CONCLUSIONS: Ac-PACAP and IK after
     the brain ischemia could pass the blood-brain barrier and protect brain
     cell damage.

L23  ANSWER 2 OF 45      MEDLINE on STN
AB   The aim of the present study was to compare in man the innervation pattern
     and the functional responses to neuronal messengers in medium sized
     lenticulostriate and branches of the posterior cerebral arteries (PCA).
     The majority of the nerve fibers found were sympathetic and displayed
     specific immunoreactivity for tyrosine hydroxylase (TH) and neuropeptide Y
     (NPY).  Only few nerve fibers displayed vasoactive intestinal polypeptide
     (VIP), calcitonin gene-related peptide (CGRP) and substance P (SP)
     immunoreactivity.  In both arteries, the contractions induced by
     noradrenaline (NA), NPY and 5-hydroxytryptamine (5-HT) and the relaxant
     responses induced by acetylcholine (ACh), VIP and pituitary adenylate
     cyclase activating peptide-27 (PACAP) as well as CGRP and SP were compared
     in vitro.  In conclusion, there was no major difference in innervation
     pattern or vasomotor sensitivity (pEC50 and pIC50 values) between the two
     vessels.  However, the general pattern indicates stronger vasomotor
     responses (Emax and Imax) in the PCA branches as compared to the
     lenticulostriate arteries which may lend support for the clinical
     observation of a difference in stroke expression between the two vascular
     areas.

L23  ANSWER 3 OF 45      MEDLINE on STN
AB   It has been reported that pituitary adenylate
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***cyclase-activating polypeptide*** (PACAP) plays an important role in preventing neuronal cell death and is also a potent vasodilator. Cerebral hypotension and hypoperfusion during cerebral ischemia and neurodegenerative diseases are well known as some of the negative factors which aggravate neuronal cell death. Nevertheless, the effect of PACAP on the cerebral circulation was not understood well. Therefore, in the present study, we determined the mean arterial blood pressure (MBP), regional cerebral blood flow (rCBF) and cerebral oxygen content (pO2) in mice, and estimated the therapeutically useful doses of PACAP. Under barbiturate anesthesia, polyethylene tubes were inserted into mice to monitor MBP and to administer PACAP (5 x 10(-13)-5 x 10(-8) mol/kg) or vasoactive intestinal peptide (VIP; 5 x 10(-12) and 5 x 10(-9) mol/kg). Then, MBP, rCBF and cerebral pO2 were simultaneously measured in the mice. PACAP (5 x 10(-10)-5 x 10(-9) mol/kg) injections transiently decreased MBP, and cerebral pO2. PACAP (5 x 10(-8) mol/kg) injections produced a long-lasting potent decline of MBP, rCBF and cerebral pO2. Therefore, PACAP should be applied at low doses which do not influence the MBP and cerebral circulation to determine the therapeutically useful doses of PACAP for neuroprotection.

L23 ANSWER 4 OF 45 MEDLINE on STN

AB The subarachnoidal cerebral blood vessels of the rat are innervated by nerve fibers containing different neuropeptides, e.g. pituitary adenylatecyclase activating polypeptide (PACAP). PACAP dilates brain arterioles and immunohistochemical studies of the rat have indicated that PACAP binds to a VPAC1-receptor in the cerebral vasculature of this species. We have investigated the perikaryal origin of the nerve fibers innervating the subarachnoidal blood vessels of the rat by combined retrograde tracing with Fluorogold and immunohistochemistry. The in vivo neuronal retrograde tracings were done by injection of 2% Fluorogold in water into the subarachnoidal space in the area of the middle cerebral artery. The retrograde transported tracer was detected by use of an antibody against Fluorogold. One week after the injections, the animals were vascularly perfused with Stephanini's fixative and labeled perikarya were found bilaterally in the trigeminal, sphenopalatine, and otic ganglia. The retrograde Fluorogold tracings were combined with immunohistochemistry for PACAP using a mouse monoclonal antibody and the biotinylated tyramide amplification system. Double labeled perikarya containing both Fluoro-gold and PACAP were found predominantly in the trigeminal ganglion, and only rarely in the otic and sphenopalatine ganglion. Summarizing, our retrograde tracings combined with immunohistochemistry indicate that the perikarya in the trigeminal ganglion are the main origin of PACAPergic nerve fibers projecting to the cerebral vasculature of the rat.

L23 ANSWER 5 OF 45 MEDLINE on STN

AB Vasoactive intestinal polypeptide (VIP) and ***pituitary adenylate cyclase activating polypeptide*** (PACAP) are closely related peptides with wide distribution in the nervous system. The aim of the present study was to investigate functional characteristics and the influence of sex steroids on the vasodilatory effects of these two peptides in cerebral and coronary vessels from female New Zealand White (NZW) rabbits.The localization and concentration of VIP and PACAP in cardiovascular tissue was evaluated using immunohistochemistry and radioimmunoassays. The vasodilatory effects of VIP and PACAP were investigated using myographs, allowing isometric tension recordings. In order to evaluate the influence of steroid hormones, the rabbits were ovariectomized and randomized to treatment for 4 weeks with 17beta-estradiol (E(2)), Norethindrone Acetate (NETA), E(2)+NETA or placebo. Ring segments of the posterior cerebral artery, the right proximal coronary artery and the distal left coronary artery were examined. The highest concentrations of VIP/PACAP were observed in cerebral and coronary arteries: 5.0/5.7 and 2.8/3.5 pmol/g, respectively. The peptides were localized in nerve fibres innervating the

arteries. Both peptides produced dose-dependent vasodilatory responses in all vessels investigated. While the effects of PACAP were identical in cerebral and coronary arterial segments, the effects of VIP displayed significant differences (E(max), pI(2), Hill-slope). Treatment with sex steroids induced no changes in the vascular effects of the two peptides.These results indicate different mechanisms of action for the vasodilating effects of the two closely related peptides VIP and PACAP in different areas of the coronary and ***cerebrovascular*** tree. Treatment with female sex steroids does not seem to change these mechanisms.

L23 ANSWER 6 OF 45 MEDLINE on STN

AB This study was designed to determine the role of altered cAMP and K(+) channel-dependent mechanisms in impaired pial artery dilation to the newly described opioid, nociceptin/orphanin FQ (NOC/oFQ) following hypoxia/ischemia in newborn pigs equipped with a closed cranial window. Recent studies have observed that NOC/oFQ elicits pial dilation via release of cAMP, which, in turn, activates the calcium sensitive (K(ca)) and the ATP-dependent K(+) (K(ATP)) channel. Global cerebral ischemia (20 min) was induced via elevation of intracranial pressure, while hypoxia (10 min) decreased pO(2) to 35+/-3 mm Hg with unchanged pCO(2). Topical NOC/oFQ (10(-8), 10(-6) M) induced vasodilation was attenuated by ischemia/reperfusion (I+R) and reversed to vasoconstriction by hypoxia/ischemia/reperfusion (H+I+R) at 1 h of reperfusion (control, 9+/-1 and 16+/-1%; I+R, 3+/-1 and 6+/-1%; H+I+R, -7+/-1 and -12+/-1%). Such altered dilation returned to control values within 4 h in I+R animals and within 12 h in H+I+R animals. NOC/oFQ dilation was associated with elevated CSF cAMP in control animals but such biochemical changes were attenuated in I+R animals and reversed to decreases in cAMP concentration in H+I+R animals (control, 1037+/-58 and 1919+/-209 fmol/ml; I+R, 1068+/-33 and 1289+/-30 fmol/ml; H+I+R, 976+/-36 and 772+/-27 fmol/ml for absence and presence of NOC/oFQ 10(-6) M, respectively). Topical 8-Bromo cAMP (10(-8), 10(-6) M) pial dilation was unchanged by I+R but blunted by H+I+R (control, 10+/-1 and 20+/-1%; I+R, 11+/-1 and 20+/-2%; H+I+R, 0+/-1 and 0+/-2%). ***Pituitary adenylate cyclase activating polypeptide*** and cromakalim, adenylate cyclase and K(ATP) channel activators, respectively, elicited dilation that was blunted by both I+R and H+I+R while NS1619, a K(ca) channel activator, elicited dilation that was unchanged by I+R but blunted by H+I+R. These data indicate that impaired NOC/oFQ dilation following I+R results form altered adenylate cyclase and K(ATP) channel-dependent mechanisms. These data further indicate that impaired NOC/oFQ dilation following H+I+R results not only from altered adenylate cyclase and K(ATP) channel but also from altered cAMP and K(ca) channel-dependent mechanisms.

L23 ANSWER 7 OF 45 MEDLINE on STN

AB ***Pituitary adenylate cyclase-activating polypeptide*** (PACAP) has been shown to be a potent neuroprotective agent in global and focal ischemia. We demonstrated that PACAP could cross the blood-brain barrier (BBB) by a saturable transport system, and a systemic administration of PACAP reduced the infarct induced by unilateral middle cerebral artery occlusion (MCAO). Therefore, we studied whether this transport system is affected by MCAO in the rat. The entry of PACAP38 into the brain was compared in five groups: control, 4, 6, 24, and 48 h after MCAO. [(125)I]PACAP38 was injected intravenously and serum and various brain regions were collected 3 min later. The rate of entry into the brain of PACAP38 was also determined. We showed that PACAP entered the rat brain via a rapid transport system when the BBB is intact. After transient (2 h) unilateral MCAO, all regions of the brain, showed a selective increase in the passage of PACAP38 across the BBB after 4 h after the occlusion, which was not related to any generalized change in the permeability of the BBB, as measured with albumin. A significant decrease in the amount of PACAP38 entering the brain was observed in the 6- and 24-h groups, but it returned

to the baseline level in the 48-h group. These results suggest that focal cerebral ischemia can selectively modify the passage of PACAP38 across the BBB, in both damaged and undamaged sides of the brain, and that these changes in influx are not solely due to the disruption of BBB. These findings imply the necessity of adjusting the dose of intravenously administered PACAP38 in order to maximize its therapeutic effect on the brain damage resulting from focal ischemia

L23 ANSWER 8 OF 45 MEDLINE on STN

AB The two structurally related peptides, vasoactive intestinal polypeptide (VIP) and ***pituitary adenylate cyclase activating polypeptide*** (PACAP), are present in cerebral vascular nerve fibers. Biologic actions of VIP are exerted through two receptors, VPAC1 and VPAC2, having similar binding affinity for both VIP and PACAP. In the current study, the authors have developed a specific antibody against the rVPAC1 receptor to examine the localization of rVPAC1 immunoreactivity in cerebral arteries and arterioles of the rat by immunohistochemistry using fluorescence confocal microscopy. Specificity of the antiserum was ensured by immunoblotting and immunocytochemistry of cells transfected with cDNA encoding the different PACAP-VIP receptor subtypes. The rVPAC1 receptor immunoreactivity was localized to the plasmalemma of circularly orientated smooth muscle cells on superficial cerebral arteries and arterioles taken from the basal surface of the brain. By double immunostaining VIP immunoreactive nerve fibers and, to a lesser extent, those containing PACAP were shown to have intimate contact with the receptor protein. Vasoactive intestinal polypeptide and PACAP containing ***cerebrovascular*** nerve fibers were found in separate nerve populations with different distribution pattern and density. In brain sections processes of cortical VIP-, but not PACAP-, containing neurons seemed to innervate the rVPAC1 receptor of pial arterioles on the brain surface. The current findings provide the neuroanatomical substrate for a role of VIP and maybe PACAP in the regulation of cerebral blood flow.

L23 ANSWER 9 OF 45 MEDLINE on STN

AB Activation of calcium sensitive (K(ca)) K channels and cAMP contribute to pial artery dilation observed during a 10-min exposure to hypoxia. Recent studies show that pial dilation during a 20- or 40-min hypoxic exposure was less than that observed during a 5- or 10-min exposure indicating that stimulus duration determines the nature of the vascular response to hypoxia. The present study was designed to determine if the stimulus duration modulates the contribution of K(ca) channel activation and cAMP-dependent mechanisms to hypoxic pial artery dilation in piglets equipped with a closed cranial window. The K(ca) channel antagonist iberiotoxin had no influence on pial dilation during 5 min of hypoxia (pO(2) approximately 25 mmHg), decremented the dilation during 10- and 20-min exposure, but had no effect on the dilation during a 40-min exposure (33+/-1% vs. 32+/-3%, 33+/-1% vs. 25+/-1%, 23+/-1% vs. 19+/-1%, and 21+/-2% vs. 17+/-2% for 5-, 10-, 20-, and 40-min hypoxic dilations before and after iberiotoxin). NS1619, a K(ca) channel agonist, induced pial dilation during hypoxia that was attenuated by 20- and 40-min but not by 5- and 10-min exposure durations. Similarly, the cAMP antagonist Rp 8-Bromo cAMPs had no influence on pial dilation during 5 min of hypoxia, decremented the dilation during a 10-min exposure, but had no effect on the dilation during a 20- or 40-min exposure (36+/-1% vs. 34+/-2%, 34+/-1% vs. 22+/-1%, 24+/-2% vs. 21+/-2%, and 21+/-2% vs. 19+/-2% for 5-, 10-, 20-, and 40-min hypoxic dilations before and after Rp 8-Bromo cAMPs). Additionally, CSF cAMP was unchanged during 5 min, elevated during 10 min, but such elevations were attenuated during 20- and 40-min hypoxic exposure. Pial vasodilation to a cAMP analogue during hypoxia was attenuated by 20- and 40-min but not by 5- and 10-min hypoxic exposure durations. These data show that K(ca) channel activation and cAMP contribute to hypoxic pial artery dilation in a stimulus duration-dependent manner. These data suggest that diminished pial artery

dilation during longer hypoxic exposure results from attenuated K(ca) channel and cAMP-dependent mechanisms.

L23 ANSWER 10 OF 45 MEDLINE on STN
AB The presence of nerve endings containing ***pituitary adenylate cyclase-activating polypeptide*** (PACAP) and vasoactive intestinal polypeptide (VIP) around cerebral microvessels suggests that these peptides have regulatory roles in the cerebral microcirculation. Prostanoids synthesized by the ***cerebrovascular*** endothelium have a determining role in the regulation of the brain circulation. In the present study, the effects of PACAP and VIP on the cyclooxygenase pathway of cerebral microvessels were investigated. The isolated microvessels were incubated with 1-14C-arachidonic acid and different concentrations of the peptides. The prostanoids formed were separated by means of overpressure thin-layer chromatography, and were quantitatively determined by liquid scintillation. Higher concentrations (10-7 and 10-6 mol L-1) of PACAP significantly inhibited the activity of the cyclooxygenase pathway, whereas VIP had no significant effect on it. As regards the cyclooxygenase metabolites, the syntheses of thromboxane A2 and prostaglandin D2 were inhibited significantly. PACAP and VIP are known to increase the intracellular cAMP level in the cerebral microvessels and in the present experiments the protein kinase A inhibitor H-89 attenuated the effect of PACAP on prostanoid synthesis. It is concluded that the cyclooxygenase pathway of rat cerebral microvessels is more sensitive to PACAP than to VIP. The inhibitory effect of PACAP on prostanoid synthesis is mediated via a cAMP-dependent pathway. By inhibiting the formation of vasoactive prostanoids, PACAP can decrease the vasoreactivity of the microvessels.

=> s l18 and l20
L24 2253 L18 AND L20

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L25 33 L24 AND ISCHEMIA

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L25 ANSWER 1 OF 33 MEDLINE on STN
AB ***Pituitary adenylate cyclase-activating polypeptide*** (PACAP) is a pleiotropic neuropeptide that belongs to the secretin/glucagon/***vasoactive intestinal peptide*** (VIP) family. PACAP prevents ischemic delayed neuronal cell death (apoptosis) in the hippocampus. PACAP inhibits the activity of the mitogen-activated protein kinase (MAPK) family, especially JNK/SAPK and p38, thereby protecting against apoptotic cell death. After the ***ischemia***-reperfusion, both pyramidal cells and astrocytes increased their expression of the PACAP receptor (PAC1-R). Reactive astrocytes increased their expression of PAC1-R, released interleukin-6 (IL-6) that is a proinflammatory cytokine with both differentiation and growth-promoting effects for a variety of target cell types, and thereby protected neurons from apoptosis. These results suggest that PACAP itself and PACAP-stimulated secretion of IL-6 synergistically inhibit apoptotic cell death in the hippocampus. The PAC1-R is expressed in the neuroepithelial cells from early developmental stages and in various brain regions during development. We have recently found that PACAP, at physiological concentrations, induces differentiation of mouse neural stem cells into astrocytes. Neural stem cells were prepared from the telencephalon of mouse embryos and cultured with basic fibroblast growth factor. The PAC1-R immunoreactivity was demonstrated in the neural stem cells. When neural stem cells were exposed to PACAP, about half of these cells showed glial fibrillary acidic protein (GFAP) immunoreactivity. This phenomenon was significantly antagonized by a

PAC1-R antagonist (PACAP6-38), indicating that PACAP induces differentiation of neural stem cell into astrocytes. Other our physiological studies have demonstrated that PACAP acts on PAC1-R in mouse neural stem cells and its signal is transmitted to the PAC1-R-coupled G protein Gq but not to Gs. These findings strongly suggest that PACAP plays very important roles in neuroprotection in adult brain as well as astrocyte differentiation during development.

L25 ANSWER 2 OF 33 MEDLINE on STN

AB ***Pituitary adenylate cyclase activating polypeptide*** (PACAP), ***vasoactive intestinal peptide*** (VIP) and peptide histidine-isoleucine (PHI), are structurally related endogenous peptides widely expressed in the central and peripheral nervous system and showing rich profile of biological activities. They act as neurotransmitters, neuromodulators and neurotrophic factors. Recently, their neuroprotective potential has been revealed in numerous in vitro and in vivo models. Thus, PACAP and VIP protected the cells from neurotoxic effects of ethanol, hydrogen peroxide (H2O2, beta-amyloid and glycoprotein 120 (gp120). Moreover, PACAP showed neuroprotection against glutamate, human prion protein fragment 106-126 [PrP(106-126)] and C2-ceramide. Both peptides reduced brain damage after ***ischemia*** and ameliorated neurological deficits in a model of Parkinson's disease. Neuroprotective potential of PHI has not been thoroughly investigated yet, but several results obtained in the last years do not exclude it. The mechanism underlying neuroprotective properties of PACAP seems to involve activation of adenylyl cyclase (AC) --> cyclic adenosine 3',5'-mono-phosphate (cAMP) --> protein kinase A (PKA) and mitogen-activated protein (MAP) kinase pathways, and inhibition of caspase-3. PACAP can also, yet indirectly, stimulate astrocytes to release neuroprotective factors, such as regulated upon activation normal T cell expressed and secreted (RANTES) and macrophage inflammatory protein 1 (MIP-1) chemokines. Neuroprotective activity of VIP seems to involve an indirect mechanism requiring astrocytes. VIP-stimulated astrocytes secrete neuroprotective proteins, including activity-dependent neurotrophic factor (ADNF) and activity-dependent neuroprotective protein (ADNP), as well as a number of cytokines. However, in the activated microglia, VIP and PACAP are capable of inhibiting the production of inflammatory mediators which can lead to neurodegenerative processes within the brain. In conclusion, studies carried out on the central nervous system have shown that PACAP, VIP, and likely PHI, are endowed with a neuroprotective potential, which renders them (or their derivatives) promising therapeutic agents in several psychoneurological disorders linked to neurodegeneration.

L25 ANSWER 3 OF 33 MEDLINE on STN

AB BACKGROUND: ***Vasoactive intestinal peptide*** (VIP),.and pituitary adenylate cyclase-activating peptide (PACAP), are members of a VIP/secretin/glucagon family. These peptides were demonstrated to possess the neuroprotective properties. However, these peptides are not suited to be developed as a medicine for brain ***ischemia*** because of their susceptibilities to endopeptidases. METHODS: We examined the effects of IK 312548 (IK), VIP derivative, and Ac-PACAP, PACAP derivative, on the 10 min two-vessel occlusion (2 VO) model in C 57 BL/6 N mice lacking a part of the posterior communicating artery, and the.30 min middle cerebral artery occlusion (MCAO) model in ICR mice. A 10 ml x kg(-1) dose of each derivative (final concentration; 1 fmol x kg(-1) and 100 pmol x kg(-1)) was injected intraperitoneally (i.p.) to each animal just after the preparation of brain ***ischemia***. RESULTS: In 2 VO experiments, the number of neuronal cells in hippocampus was significantly reduced. However IK and Ac-PACAP treatments inhibited such reductions of neuronal cells in a dose-dependent manner. Particularly, between 1 pmol x kg(-1) and 100 pmol x kg(-) IK, and also between 10 fmol x kg(-1) and 1 pmol x kg(-1) Ac-PACAP significantly protected neuronal cell loss. In MCAO experiments, more than 60% of

hemisphere was damaged. By treatment of IK (1-100 pmol x kg(-1)) and Ac-PACAP (1 fmol-1 pmol x kg(-1)), the range of brain damage decreased in a dose-dependent manner. CONCLUSIONS: Ac-PACAP and IK after the brain ***ischemia*** could pass the blood-brain barrier and protect brain cell damage.

L25 ANSWER 4 OF 33 MEDLINE on STN

AB AIM: Pituitary adenylate cyclase activating-peptide (PACAP) is a late member of the secretin/glucagon/***vasoactive intestinal peptide*** (VIP) family of brain-gut peptides. It is unknown whether PACAP takes part in the development of acute pancreatitis and whether PACAP or its antagonists can be used to suppress the progression of acute pancreatitis. We investigated the actions of PACAP and its receptor antagonists in acute pancreatitis on rats. METHODS: Acute pancreatitis was induced in rats with caerulein or 3.5% sodium taurocholate. The rats were continuously infused with 5-30 microg/kg PACAP via jugular vein within the first 90 min, while 10-100 microg/kg PACAP6-27 and (4-Cl-D-Phe6, Leu17) VIP (PACAP receptor antagonists) were intravenously infused for 1 h. Biochemical and histopathological assessments were made at 4 h after infusion. Pancreatic and duodenal PACAP concentrations were determined by enzyme-linked immunosorbent assay (ELISA). Chinese ink-perfused pancreas was fixed, sectioned and cleared for counting the functional capillary density. RESULTS: PACAP augmented caerulein-induced pancreatitis and failed to ameliorate sodium taurocholate-induced pancreatitis. ELISA revealed that relative concentrations of PACAP in pancreas and duodenum were significantly increased in both sodium taurocholate- and caerulein-induced pancreatitis compared with those in normal controls. Unexpectedly, PACAP6-27 and (4-Cl-D-Phe6, Leu17) VIP could induce mild acute pancreatitis and aggravate caerulein-induced pancreatitis with characteristic manifestations of acute hemorrhagic/necrotizing pancreatitis. Functional capillary density of pancreas was interpreted in the context of pancreatic edema, and calibrated functional capillary density (calibrated FCD), which combined measurement of functional capillary density with dry weight/wet weight ratio, was introduced. Hyperemia or congestion, rather than ***ischemia***, characterized pancreatic microcirculatory changes in acute pancreatitis. CONCLUSION: PACAP may take part in the pathogenesis of acute pancreatitis in rats. The two PACAP receptor antagonsits might act as partial agonists. Calibrated functional capillary density can reflect pancreatic microcirculatory changes in acute pancreatitis.

L25 ANSWER 5 OF 33 MEDLINE on STN

AB ***Pituitary adenylate cyclase-activating polypeptide*** (PACAP), ***vasoactive intestinal peptide*** (VIP), and peptide histidine-isoleucine (PHI) belong to a structurally related family of polypeptides present in many regions of the central and peripheral nervous system. The neuroprotective potential of PACAP, VIP, and PHI has become a matter of intensive investigations in many animal models. In vitro studies revealed that PACAP protects neurons against apoptosis occurring naturally during CNS development and apoptosis induced by a series of neurotoxins, such as ethanol, hydrogen peroxide (H2O2), prion protein, beta-amyloid, HIV envelope glycoprotein (gp120), potassium ion deficit, and high glutamate concentrations. Similarly, in vivo investigations conducted in models of ***ischemia*** and Parkinson's disease confirmed the neuroprotective properties of PACAP. It was revealed that the anti-apoptotic action of PACAP can be directly associated with the activation of signal transduction pathways preventing apoptosis in neurons or involve glial cells capable of releasing other neuroprotective factors affecting neurons. In contrast to PACAP, the neuroprotective action of VIP depends mainly on stimulation of astrocytes to produce and secrete factors of extremely high neuroprotective potential, including activity-dependent neurotrophic factor (ADNF) and activity-dependent neuroprotective protein (ADNP). It was shown that ADNF and ADNP, as well

as their shortened derivatives ADNF-9 and NAP, prevent neurons from electrical blockade, excitotoxicity, apoE deficiency, glucose deficit, ***ischemia***, toxic action of ethanol, beta-amyloid, and gp120. The neuroprotective potential of PHI has not been as thoroughly investigated yet, but recent data have confirmed that this peptide can also function as a neuroprotectant. It is thought that PACAP, VIP, and possibly PHI may serve as a goal of modern therapeutic strategies in various neurodegenerative disorders.

L25 ANSWER 6 OF 33 MEDLINE on STN

AB It has been reported that ***pituitary adenylate cyclase-activating polypeptide*** (PACAP) plays an important role in preventing neuronal cell death and is also a potent vasodilator. Cerebral hypotension and hypoperfusion during cerebral ***ischemia*** and neurodegenerative diseases are well known as some of the negative factors which aggravate neuronal cell death. Nevertheless, the effect of PACAP on the cerebral circulation was not understood well. Therefore, in the present study, we determined the mean arterial blood pressure (MBP), regional cerebral blood flow (rCBF) and cerebral oxygen content (pO2) in mice, and estimated the therapeutically useful doses of PACAP. Under barbiturate anesthesia, polyethylene tubes were inserted into mice to monitor MBP and to administer PACAP (5 x 10(-13)-5 x 10(-8) mol/kg) or ***vasoactive intestinal peptide*** (VIP; 5 x 10(-12) and 5 x 10(-9) mol/kg). Then, MBP, rCBF and cerebral pO2 were simultaneously measured in the mice. PACAP (5 x 10(-10)-5 x 10(-9) mol/kg) injections transiently decreased MBP, and cerebral pO2. PACAP (5 x 10(-8) mol/kg) injections produced a long-lasting potent decline of MBP, rCBF and cerebral pO2. Therefore, PACAP should be applied at low doses which do not influence the MBP and cerebral circulation to determine the therapeutically useful doses of PACAP for neuroprotection.

L25 ANSWER 7 OF 33 MEDLINE on STN

AB ***Pituitary adenylate cyclase activating polypeptide*** (PACAP) modulates neurotransmission in the central and peripheral nervous systems. In vitro and in vivo studies have shown the protective effects of PACAP against neuronal damage induced by ***ischemia*** and agonists of NMDA-type glutamate receptors. Here, we demonstrated that PACAP also protected against neuronal toxicity induced by beta-amyloid (Abeta) peptide, aggregation of which is a causative factor for Alzheimer's disease. PACAP (10(-9)M) rescued 80% of decreased cell viability and 50% of elevated caspase-3 activity that resulted from exposure of PC12 cells to Abeta. PACAP was at least 10(4)-fold more effective than other neuropeptides including ***vasoactive intestinal peptide*** (VIP) and humanin, which correlated with the level of cAMP accumulation. Thus, our results suggested that PACAP attenuates Abeta-induced cell death in PC12 cells through an increase in cAMP and that caspase-3 deactivation by PACAP is involved in the signaling pathway for this neuroprotection. 

L25 ANSWER 8 OF 33 MEDLINE on STN

AB Both ***vasoactive intestinal peptide*** (VIP) and ***pituitary adenylate cyclase-activating polypeptide*** (PACAP) act as neurotransmitters in the central and peripheral nervous systems. Attention has been focused on these neuropeptides because among their numerous biological activities, they have been confirmed to show neuroprotective effects against ***ischemia*** and glutamate-induced cytotoxicity. It is well established that glutamate has excitatory effects on neuronal cells, and that excessive glutamate shows potent neurotoxicity, especially in neuronal nitric oxide synthase-containing neurons. Glutamate stimulates the production of nitric oxide (NO) in neurons, and the NO generated is tightly associated with the delayed death of neurons. We examined the effects of these neuropeptides on the glutamate-induced neural actions

using PC12 cells, and we confirmed the important activities of PACAP/VIP on the production of NO as well as the delayed cell death stimulated by glutamate.

L25 ANSWER 9 OF 33 MEDLINE on STN
AB OBJECTIVES: ***Pituitary adenylate cyclase activating polypeptide*** (PACAP) and vasoactive intestinal polypeptide (VIP) belong to the same peptide family, and both neuropeptides have been shown to exert in vitro and in vivo neurotrophic and neuroprotective effects. The aim of the present study was to investigate and compare the protective effects of PACAP and VIP in permanent focal cerebral ***ischemia*** in rats. The effect on the progression of the cerebral infarct was also studied. METHOD: Male rats were injected 450 pmol PACAP or VIP dissolved in physiological saline intracerebroventricularly, preceding the occlusion of the middle cerebral artery. Control animals received vehicle treatment. Permanent focal ***ischemia*** was induced by the intraluminal filament occlusion of the middle cerebral artery. Animals were sacrificed 12 or 24 hours after the onset of ***ischemia***, and infarcted brain areas were determined by staining bran sections with triphenyl-tetrazolium chloride. RESULTS: Twelve hours after ***ischemia***, the infarcted brain volume resulted to be 14.8% in the control group, 15.3% in the VIP-treated group and 5.8% in the PACAP-treated animals. Twenty-four hours after middle cerebral artery occlusion, the infarcted brain volumes were 21.5%, 20.7% and 14.3% in the control, VIP and PACAP-treated animals, respectively. CONCLUSION: Our results provide further evidence for the neuroprotective effects of PACAP38 as given in form of a preischemic bolus. It slows down the progression of the evolution of the infarct and reduces the final infarct size. In contrast, a related peptide, VIP, does not have neuroprotective effects under the same experimental conditions.

L25 ANSWER 10 OF 33 MEDLINE on STN
AB ***Vasoactive intestinal peptide*** (VIP) is a neuropeptide synthesized by immune cells that can modulate several immune aspects, including the function of cells involved in the inflammatory response, such as macrophages and monocytes. The production and release of cytokines by activated phagocytes are important events in the pathogenesis of ***ischemia***-reperfusion injury. There is abundant evidence that the proinflammatory cytokine TNF-alpha is an important mediator of shock and organ failure complicating Gram-negative sepsis. VIP has been shown to attenuate the deleterious consequences of this pathologic phenomenon. In this study we have investigated the effects of VIP and the structurally related neuropeptide ***pituitary adenylate cyclase-activating polypeptide*** (PACAP38) on the production of TNF-alpha by endotoxin-activated murine peritoneal macrophages. Both neuropeptides rapidly and specifically inhibit the LPS-stimulated production of TNF-alpha, exerting their action through the binding to VPAC1 receptor and the subsequent activation of the adenylate cyclase system. VIP and PACAP regulate the production of TNF-alpha at a transcriptional level. In vitro results were correlated with an inhibition of both TNF-alpha expression and release in endotoxemic mice in vivo. The immunomodulatory role of VIP in vivo is supported by the up-regulation of VIP release in serum and peritoneal fluid by LPS and proinflammatory cytokines such as TNF-alpha, IL-1beta, and IL-6. These findings support the idea that under toxicity conditions associated with high LPS doses, VIP and PACAP could act as protective mediators that regulate the excessive release of TNF-alpha to reduce inflammation or shock.

L25 ANSWER 11 OF 33 MEDLINE on STN
AB ***Vasoactive intestinal peptide*** (VIP) is a neuropeptide synthesized by immune cells that can modulate several immune aspects, including the function of cells involved in the inflammatory response, such as macrophages and monocytes. Production and release of

cytokines by activated mononuclear phagocytes is an important event in the pathogenesis of ***ischemia***-reperfusion injury. VIP has been shown to attenuate the deleterious consequences of this pathologic phenomenon. We have investigated the effects of VIP and PACAP38 on the production of interleukin-6 (IL-6), a proinflammatory cytokine, by endotoxin-activated murine macrophages. Both neuropeptides exhibit a dual effect on the IL-6 production by peritoneal macrophages. Whereas VIP and PACAP inhibit with similar dose-response curves the release of IL-6 from macrophages stimulated with a LPS dose range from 100 pg/mL to 10 microg/mL, both neuropeptides enhance IL-6 secretion in unstimulated macrophages and in macrophages stimulated with very low LPS concentrations (1-10 pg/mL). The inhibition on LPS-induced IL-6 production is specific, presumably mediated through a subtype of the PACAP-R. VIP and PACAP regulate the production of IL-6 at a transcriptional level. These results were correlated with an inhibition on both IL-6 expression and release in endotoxemic mice in vivo. These findings support the idea that in the absence of stimulation or in the presence of low doses of LPS, VIP and PACAP could play a role in immune system homeostasis. However, under toxicity conditions associated with high LPS doses, VIP and PACAP could act as protective mediators that regulate the excessive release of IL-6 in order to reduce inflammation or shock.

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AB ***Pituitary adenylate cyclase-activating polypeptide*** (PACAP) is a pleiotropic neuropeptide that belongs to the secretin/glucagon/***vasoactive intestinal peptide*** (VIP) family. PACAP prevents ischemic delayed neuronal cell death (apoptosis) in the hippocampus. PACAP inhibits the activity of the mitogen-activated protein kinase (MAPK) family, especially JNK/SAPK and p38, thereby protecting against apoptotic cell death. After the ***ischemia***-reperfusion, both pyramidal cells and astrocytes increased their expression of the PACAP receptor (PAC1-R). Reactive astrocytes increased their expression of PAC1-R, released interleukin-6 (IL-6) that is a proinflammatory cytokine with both differentiation and growth-promoting effects for a variety of target cell types, and thereby protected neurons from apoptosis. These results suggest that PACAP itself and PACAP-stimulated secretion of IL-6 synergistically inhibit apoptotic cell death in the hippocampus. The PAC1-R is expressed in the neuroepithelial cells from early developmental stages and in various brain regions during development. We have recently found that PACAP, at physiological concentrations, induces differentiation of mouse neural stem cells into astrocytes. Neural stem cells were prepared from the telencephalon of mouse embryos and cultured with basic fibroblast growth factor. The PAC1-R immunoreactivity was demonstrated in the neural stem cells. When neural stem cells were exposed to PACAP, about half of these cells showed glial fibrillary acidic protein (GFAP) immunoreactivity. This phenomenon was significantly antagonized by a PAC1-R antagonist (PACAP6-38), indicating that PACAP induces differentiation of neural stem cell into astrocytes. Other our physiological studies have demonstrated that PACAP acts on PAC1-R in mouse neural stem cells and its signal is transmitted to the PAC1-R-coupled G protein Gq but not to Gs. These findings strongly suggest that PACAP plays very important roles in neuroprotection in adult brain as well as astrocyte differentiation during development.

L25 ANSWER 13 OF 33 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

AB ***Pituitary adenylate cyclase activating polypeptide*** (PACAP), ***vasoactive intestinal peptide*** (VIP) and peptide his histidine-isoleucine (PHI), are structurally related endogenous peptides widely expressed in the central and peripheral nervous system and showing rich profile of biological activities. They act as neurotransmitters,

neuromodulators and neurotrophic factors. Recently, their neuroprotective potential has been revealed in numerous in vitro and in vivo models. Thus, PACAP and VIP protected the cells,from neurotoxic effects of ethanol, hydrogen peroxide (H2O2), P-amyloid and glycoprotein 120 (gp120). Moreover, PACAP showed neuroprotection against glutamate, human prion protein fragment 106-126 [PrP(106-126)] and C2-ceramide. Both peptides reduced brain damage after ***ischemia*** and ameliorated neurological deficits in a model of Parkinson's disease. Neuroprotective potential of PHI has not been thoroughly investigated yet, but several results obtained in the last years do not exclude it. The mechanism underlying neuroprotective properties of PACAP seems to involve activation of adenylyl cyclase (AC) -> cyclic adenosine 3',5'-mono-phosphate (cAMP) -> protein kinase A (PKA) and mitogen-activated protein (MAP) kinase pathways, and inhibition of caspase-3. PACAP can also, yet indirectly, stimulate astrocytes to release neuroprotective factors, such as regulated upon activation normal T cell expressed and secreted (RANTES) and macrophage inflammatory protein I (MIP-1) chemokines. Neuroprotective activity of VIP seems to involve an indirect mechanism requiring astrocytes. VIP-stimulated astrocytes secrete neuroprotective proteins, including activity-dependent neurotrophic factor (ADNF) and activity-dependent neuroprotective protein (ADNP), as well as a number of cytokines. However, in the activated microglia, VIP and PACAP are capable of inhibiting the production of inflammatory mediators which can lead to neurodegenerative processes within the brain.In conclusion, studies carried out on the central nervous system have shown that PACAP, VIP, and likely PHI, are endowed with a neuroprotective potential, which renders them (or their derivatives) promising therapeutic agents, in several psychoneurological disorders linked to neurodegeneration.

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L25 ANSWER 15 OF 33 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

AB It has been reported that ***pituitary adenylate cyclase-activating polypeptide*** (PACAP) plays an important role in preventing neuronal cell death and is also a potent vasodilator. Cerebral hypotension and hypoperfusion during cerebral ***ischemia*** and neurodegenerative diseases are well known as some of the negative factors which aggravate neuronal cell death. Nevertheless, the effect of PACAP on the cerebral circulation was not understood well. Therefore, in the present study, we determined the mean arterial blood pressure (MBP), regional cerebral blood flow (rCBF) and cerebral oxygen content (pO2) in mice, and estimated the therapeutically useful doses of PACAP. Under barbiturate anesthesia,. polyethylene tubes were inserted into mice to monitor MBP and to administer PACAP (5 x 10-13 -5 x 10-8 mol/kg) or ***vasoactive intestinal peptide*** (VIP; 5 X 10-12 and 5 X 10-9 mol/kg). Then, MBP, rCBF and cerebral pO2 were simultaneously measured in the mice. PACAP (5. x 10-10 -5 x 10-9 mol/kg) injections transiently decreased MBP, and cerebral pO2. PACAP (5 X 10- 8 mol/kg) injections produced a long-lasting potent decline of N113P, rCBF and cerebral pO2. Therefore, PACAP should be applied at low doses which do not influence the MBP and cerebral circulation to determine the therapeutically useful doses of PACAP for neuroprotection. 

L25 ANSWER 16 OF 33 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

AB Both ***vasoactive intestinal peptide*** (VIP) and ***pituitary adenylate cyclase-activating polypeptide*** (PACAP) act as neurotransmitters in the central and peripheral nervous systems. Attention has been focused on these neuropeptides because among their numerous biological activities, they have been confirmed to show neuroprotective effects against

***ischemia*** and glutamate-induced cytotoxicity. It is well established that glutamate has excitatory effects on neuronal cells, and that excessive glutamate shows potent neurotoxicity, especially in neuronal nitric oxide synthase-containing neurons. Glutamate stimulates the production of nitric oxide (NO) in neurons, and the NO generated is tightly associated with the delayed death of neurons. We examined the effects of these neuropeptides on the glutamate-induced neural actions using PC12 cells, and we confirmed the important activities of PACAP/VIP on the production of NO as well as the delayed cell death stimulated by glutamate.

L25 ANSWER 17 OF 33 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

AB ***Pituitary adenylate cyclase activating polypeptide*** (PACAP) modulates neurotransmission in the central and peripheral nervous systems. In vitro and in vivo studies have shown the protective effects of PACAP against neuronal damage induced by ***ischemia*** and agonists of NMDA-type glutamate receptors. Here, we demonstrated that PACAP also protected against neuronal toxicity induced by beta-amyloid (Abeta) peptide, aggregation of which is a causative factor for Alzheimer's disease. PACAP (10-9 M) rescued 80% of decreased cell viability and 50% of elevated caspase-3 activity that resulted from exposure of PC12 cells to Abeta. PACAP was at least 104-fold more effective than other neuropeptides including ***vasoactive intestinal peptide*** (VIP) and humanin, which correlated with the level of cAMP accumulation. Thus, our results suggested that PACAP attenuates Abeta-induced cell death in PC12 cells through an increase in cAMP and that caspase-3 deactivation by PACAP is involved in the signaling pathway for this neuroprotection.

L25 ANSWER 18 OF 33 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

AB ***Vasoactive intestinal peptide*** (VIP) is a neuropeptide synthesized by immune cells that can modulate several immune aspects, including the function of cells involved in the inflammatory response, such as macrophages and monocytes. Production and release of cytokines by activated mononuclear phagocytes is an important event in the pathogenesis of ***ischemia***-reperfusion injury. VIP has been shown to attenuate the deleterious consequences of this pathologic phenomenon. We have investigated the effects of VIP and PACAP38 on the production of interleukin-6 (IL-6), a proinflammatory cytokine, by endotoxin-activated murine macrophages. Both neuropeptides exhibit a dual effect on the IL-6 production by peritoneal macrophages. Whereas VIP and PACAP inhibit with similar dose-response curves the release of IL-6 from macrophages stimulated with a LPS dose range from 100 pg/mL to 10 mug/mL, both neuropeptides enhance IL-6 secretion in unstimulated macrophages and in macrophages stimulated with very low LPS concentrations (1-10 pg/mL). The inhibition on LPS-induced IL-6 production is specific, presumably mediated through a subtype of the PACAP-R. VIP and PACAP regulate the production of IL-6 at a transcriptional level. These results were correlated with an inhibition on both IL-6 expression and release in endotoxemic mice in vivo. These findings support the idea that in the absence of stimulation or in the presence of low doses of LPS, VIP and PACAP could play a role in immune system homeostasis. However, under toxicity conditions associated with high LPS doses, VIP and PACAP could act as protective mediators that regulate the excessive release of IL-6 in order to reduce inflammation or shock.

L25 ANSWER 19 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AB ***Pituitary adenylate cyclase-activating polypeptide*** (PACAP) is a pleiotropic neuropeptide that belongs to the secretin/glucagon/***vasoactive intestinal peptide*** (VIP) family. PACAP prevents ischemic delayed neuronal cell death (apoptosis) in the hippocampus.

PACAP inhibits the activity of the mitogen-activated protein kinase (MAPK) family, especially JNK/SAPK and p38, thereby protecting against apoptotic cell death. After the ***ischemia***-reperfusion, both pyramidal cells and astrocytes increased their expression of the PACAP receptor (PAC1-R). Reactive astrocytes increased their expression of PAC1-R, released interleukin-6 (IL-6) that is a proinflammatory cytokine with both differentiation and growth-promoting effects for a variety of target cell types, and thereby protected neurons from apoptosis. These results suggest that PACAP itself and PACAP-stimulated secretion of IL-6 synergistically inhibit apoptotic cell death in the hippocampus. The PAC1-R is expressed in the neuroepithelial cells from early developmental stages and in various brain regions during development. We have recently found that PACAP, at physiol. concns., induces differentiation of mouse neural stem cells into astrocytes. Neural stem cells were prepared from the telencephalon of mouse embryos and cultured with basic fibroblast growth factor. The PAC1-R immunoreactivity was demonstrated in the neural stem cells. When neural stem cells were exposed to PACAP, about half of these cells showed glial fibrillary acidic protein (GFAP) immunoreactivity. This phenomenon was significantly antagonized by a PAC1-R antagonist (PACAP6-38), indicating that PACAP induces differentiation of neural stem cell into astrocytes. Other our physiol. studies have demonstrated that PACAP acts on PAC1-R in mouse neural stem cells and its signal is transmitted to the PAC1-R-coupled G protein Gq but not to Gs. These findings strongly suggest that PACAP plays very important roles in neuroprotection in adult brain as well as astrocyte differentiation during development.

L25 ANSWER 20 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AB A review. ***Pituitary adenylate cyclase activating polypeptide*** (PACAP), ***vasoactive intestinal peptide*** (VIP) and peptide histidine-isoleucine (PHI), are structurally related endogenous peptides widely expressed in the central and peripheral nervous system and showing rich profile of biol. activities. They act as neurotransmitters, neuromodulators and neurotrophic factors. Recently, their neuroprotective potential has been revealed in numerous in vitro and in vivo models. Thus, PACAP and VIP protected the cells from neurotoxic effects of ethanol, hydrogen peroxide (H2O2), β-amyloid and glycoprotein 120 (gp120). Moreover, PACAP showed neuroprotection against glutamate, human prion protein fragment 106-126 [PrP(106-126)] and C2-ceramide. Both peptides reduced brain damage after ***ischemia*** and ameliorated neurol. deficits in a model of Parkinson's disease. Neuroprotective potential of PHI has not been thoroughly investigated yet, but several results obtained in the last years do not exclude it. The mechanism underlying neuroprotective properties of PACAP seems to involve activation of adenylyl cyclase (AC) → cyclic adenosine 3',5'-mono-phosphate (cAMP) → protein kinase A (PKA) and mitogen-activated protein (MAP) kinase pathways, and inhibition of caspase-3. PACAP can also, yet indirectly, stimulate astrocytes to release neuroprotective factors, such as regulated upon activation normal T cell expressed and secreted (RANTES) and macrophage inflammatory protein 1 (MIP-1) chemokines. Neuroprotective activity of VIP seems to involve an indirect mechanism requiring astrocytes. VIP-stimulated astrocytes secrete neuroprotective proteins, including activity-dependent neurotrophic factor (ADNF) and activity-dependent neuroprotective protein (ADNP), as well as a number of cytokines. However, in the activated microglia, VIP and PACAP are capable of inhibiting the production of inflammatory mediators which can lead to neurodegenerative processes within the brain. In conclusion, studies carried out on the central nervous system have shown that PACAP, VIP, and likely PHI, are endowed with a neuroprotective potential, which renders them (or their derivs.) promising therapeutic agents in several psychoneurol. disorders linked to neurodegeneration.

L25 ANSWER 21 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AB Pituitary adenylate cyclase activating-peptide (PACAP) is a late member of the secretin/glucagon/***vasoactive intestinal peptide*** (VIP) family of brain-gut peptides. It is unknown whether PACAP takes part in the development of acute pancreatitis and whether PACAP or its antagonists can be used to suppress the progression of acute pancreatitis. We investigated the actions of PACAP and its receptor antagonists in acute pancreatitis on rats. Acute pancreatitis was induced in rats with caerulein or 3.5% sodium taurocholate. The rats were continuously infused with 5-30 μg/kg PACAP via jugular vein within the first 90 min, while 10-100 μg/kg PACAP6-27 and (4-Cl-DLPhe6, Leu17) VIP (PACAP receptor antagonists) were i.v. infused for 1 h. Biochem. and histopathol. assessments were made at 4 h after infusion. Pancreatic and duodenal PACAP concns. were determined by ELISA. Chinese ink-perfused pancreas was fixed, sectioned and cleared for counting the functional capillary d. PACAP augmented caerulein-induced pancreatitis and failed to ameliorate sodium taurocholate-induced pancreatitis. ELISA revealed that relative concns. of PACAP in pancreas and duodenum were significantly increased in both sodium taurocholate- and caerulein-induced pancreatitis compared with those in normal controls. Unexpectedly, PACAP6-27 and (4-Cl-D-Phe6, Leu17) VIP could induce mild acute pancreatitis and aggravate caerulein-induced pancreatitis with characteristic manifestations of acute hemorrhagic/necrotizing pancreatitis. Functional capillary d. of pancreas was interpreted in the context of pancreatic edema, and calibrated functional capillary d. (calibrated FCD), which combined measurement of functional capillary d. with dry weight/wet weight ratio, was introduced. Hyperemia or congestion, rather than ***ischemia***, characterized pancreatic microcirculatory changes in acute pancreatitis. PACAP may take part in the pathogenesis of acute pancreatitis in rats. The two PACAP receptor antagonists might act as partial agonists. Calibrated functional capillary d. can reflect pancreatic microcirculatory changes in acute pancreatitis.

L25 ANSWER 22 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AB The invention discloses methods for promoting neurogenesis by contacting neuronal tissue with intracellular cAMP-elevating agents and intracellular calcium ion-elevating agents. Agents for promoting neurogenesis are also disclosed.

L25 ANSWER 23 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN

AB A transient increase in skin blood flow in response to an innocuous local pressure application, defined as pressure-induced vasodilatation (PIV), delays the occurrence of ***ischemia***, suggesting a protective feature against applied pressure. The PIV response depends on capsaicin-sensitive nerve fibers and calcitonin gene-related peptide (CGRP) has been shown to be involved. In these fibers, CGRP coexists with ***pituitary adenylate cyclase-activating polypeptide*** (PACAP). Three distinct receptors mediate the biol. effects of PACAP: VPAC1 and VPAC2 receptors binding with the same affinity for PACAP and ***vasoactive intestinal peptide*** and PAC1 receptors showing high selectivity for PACAP. Because the receptors are widely expressed in the nervous system and in the skin, the authors hypothesized that at least one of them is involved in PIV development. To verify this hypothesis, the authors used [D-p-Cl-Phe6,Leu17]-VIP (non-specific antagonist of VPAC1/VPAC2 receptors), PG 97-269 (antagonist of VPAC1 receptors), PACAP(6-38) (antagonist of VPAC2/PAC1 receptors) and Max.d.4 (antagonist of PAC1 receptors) in anesthetized rodents. The blockade of VPAC1/VPAC2, VPAC1 or VPAC2/PAC1 receptors eliminated the PIV response, whereas PAC1 blockade had no effect, demonstrating an involvement of VPAC1/VPAC2 receptors in PIV development. Moreover, endothelium-independent and -dependent vasodilator responses were unchanged by the VPAC1/VPAC2 antagonist. Thus, the absence of a PIV response following VPAC1/VPAC2 blockade cannot be explained by any dysfunction of the vascular smooth muscle or endothelial vasodilator capacity. The involvement of VPAC1/VPAC2 receptors in the

development of PIV seems to imply a series relationship in which each receptor type (CGRP, VPAC1, VPAC2) is necessary for the full transmission of the response.

L25 ANSWER 24 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AB ***Pituitary adenylate cyclase activating polypeptide*** (PACAP) modulates neurotransmission in the central and peripheral nervous systems. In vitro and in vivo studies have shown the protective effects of PACAP against neuronal damage induced by ***ischemia*** and agonists of NMDA-type glutamate receptors. Here, we demonstrated that PACAP also protected against neuronal toxicity induced by β-amyloid (Aβ) peptide, aggregation of which is a causative factor for Alzheimer's disease. PACAP (10-9 M) rescued 80% of decreased cell viability and 50% of elevated caspase-3 activity that resulted from exposure of PC12 cells to Aβ. PACAP was at least 104-fold more effective than other neuropeptides including ***vasoactive intestinal peptide*** (VIP) and humanin, which correlated with the level of cAMP accumulation. Thus, our results suggested that PACAP attenuates Aβ-induced cell death in PC12 cells through an increase in cAMP and that caspase-3 deactivation by PACAP is involved in the signaling pathway for this neuroprotection.

L25 ANSWER 25 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AB Both ***vasoactive intestinal peptide*** (VIP) and ***pituitary adenylate cyclase-activating polypeptide*** (PACAP) act as neurotransmitters in the central and peripheral nervous systems. Attention has been focused on these neuropeptides because among their numerous biol. activities, they have been confirmed to show neuroprotective effects against ***ischemia*** and glutamate-induced cytotoxicity. It is well established that glutamate has excitatory effects on neuronal cells, and that excessive glutamate shows potent neurotoxicity, especially in neuronal nitric oxide synthase-containing neurons. Glutamate stimulates the production of nitric oxide (NO) in neurons, and the NO generated is tightly associated with the delayed death of neurons. We examined the effects of these neuropeptides on the glutamate-induced neural actions using PC12 cells, and we confirmed the important activities of PACAP/VIP on the production of NO as well as the delayed cell death stimulated by glutamate.

L25 ANSWER 26 OF 33 CAPLUS COPYRIGHT 2007 ACS on STN
AB ***Vasoactive intestinal peptide*** (VIP) is a neuropeptide synthesized by immune cells that can modulate several immune aspects, including the function of cells involved in the inflammatory response, such as macrophages and monocytes. The production and release of cytokines by activated phagocytes are important events in the pathogenesis of ***ischemia***-reperfusion injury. There is abundant evidence that the proinflammatory cytokine TNF-α is an important mediator of shock and organ failure complicating Gram-neg. sepsis. VIP has been shown to attenuate the deleterious consequences of this pathol. phenomenon. In this study we have investigated the effects of VIP and the structurally related neuropeptide ***pituitary adenylate cyclase-activating polypeptide*** (PACAP38) on the production of TNF-α by endotoxin-activated murine peritoneal macrophages. Both neuropeptides rapidly and specifically inhibit the LPS-stimulated production of TNF-α, exerting their action through the binding to VPAC1 receptor and the subsequent activation of the adenylate cyclase system. VIP and PACAP regulate the production of TNF-α at a transcriptional level. In vitro results were correlated with an inhibition of both TNF-α expression and release in endotoxemic mice in vivo. The immunomodulatory role of VIP in vivo is supported by the up-regulation of VIP release in serum and peritoneal fluid by LPS and proinflammatory cytokines such as TNF-α, IL-1β, and IL-6.

These findings support the idea that under toxicity conditions associated with high LPS doses, VIP and PACAP could act as protective mediators that regulate the excessive release of TNF-α to reduce inflammation or shock.

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AB ***Pituitary adenylate cyclase-activating polypeptide*** (PACAP) is a pleiotropic neuropeptide that belongs to the secretin/glucagon/***vasoactive intestinal peptide*** (VIP) family. PACAP prevents ischemic delayed neuronal cell death (apoptosis) in the hippocampus. PACAP inhibits the activity of the mitogen-activated protein kinase (MAPK) family, especially JNK/SAPK and p38, thereby protecting against apoptotic cell death. After the ***ischemia***-reperfusion, both pyramidal cells and astrocytes increased their expression of the PACAP receptor (PAC1-R). Reactive astrocytes increased their expression of PAC1-R, released interleukin-6 (IL-6) that is a proinflammatory cytokine with both differentiation and growth-promoting effects for a variety of target cell types, and thereby protected neurons from apoptosis. These results suggest that PACAP itself and PACAP-stimulated secretion of IL-6 synergistically inhibit apoptotic cell death in the hippocampus. The PAC1-R is expressed in the neuroepithelial cells from early developmental stages and in various brain regions during development. We have recently found that PACAP, at physiological concentrations, induces differentiation of mouse neural stem cells into astrocytes. Neural stem cells were prepared from the telencephalon of mouse embryos and cultured with basic fibroblast growth factor. The PAC1-R immunoreactivity was demonstrated in the neural stem cells. When neural stem cells were exposed to PACAP, about half of these cells showed glial fibrillary acidic protein (GFAP) immunoreactivity. This phenomenon was significantly antagonized by a PAC1-R antagonist (PACAP6-38), indicating that PACAP induces differentiation of neural stem cell into astrocytes. Other our physiological studies have demonstrated that PACAP acts on PAC1-R in mouse neural stem cells and its signal is transmitted to the PAC1-R-coupled G protein Gq but not to Gs. These findings strongly suggest that PACAP plays very important roles in neuroprotection in adult brain as well as astrocyte differentiation during development. .COPYRGT. 2006 New York Academy of Sciences.

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AB Autoimmune dysfunction of certain vasoactive neuropeptides (VNs) has been postulated as a contributing cause of sudden infant death syndrome (SIDS), chronic fatigue syndrome (CFS), Gulf War syndrome (GWS) and other fatigue-related disorders. This family of VNs includes ***pituitary adenylate cyclase activating polypeptide*** (PACAP), ***vasoactive intestinal peptide*** (VIP) and calcitonin gene related peptide (CGRP). The postulated mechanism is compromise of adenylate cyclase activation, a vital and unique step in cyclic AMP production from ATP, through autoimmune dysfunction of VNs, their receptors or their genes possibly involving cytosine-phosphate-guanine (CpG) fragments. CpG fragments are immunomodulatory dinucleotides serving as 'friend or foe' recognition systems to differentiate bacterial and viral (hypomethylated CpG) from mammalian (methylated CpG) DNA. However hypomethylation disorders affecting these fragments in mammals may convert them to dysfunctional states by promoting autoimmune inflammatory reactions. Epigenetic mechanisms acting on gene promoter regions may contribute to the development of VN autoimmune fatigue-related disorders through CpG fragments located in vital segments of VN/receptor genes by causing signalling defects with profound implications for VN function. Neurotransmitter dysfunction particularly glutamatergic transmission could also result with disruption of neuronal cellular biochemical functions

such as ammonia regulation. Endosomal acidity and mitochondrial membrane potential modifiers such as chloroquine, together with immunoregulatory therapies, may have therapeutic implications in protecting against these apparent autoimmune disorders. This paper examines specific epigenetic and biochemical mechanisms possibly mediated by VN or receptor genes resulting in postulated VN autoimmune fatigue-related disorders. These mechanisms may have implications for treatment and prevention options for VN autoimmune disorders. VN autoimmune processes have implications for military medicine where radiological, chemical and biological agents may play an important role in pathogenesis.

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AB It has been reported that ***pituitary adenylate cyclase-activating polypeptide*** (PACAP) plays an important role in preventing neuronal cell death and is also a potent vasodilator. Cerebral hypotension and hypoperfusion during cerebral ***ischemia*** and neurodegenerative diseases are well known as some of the negative factors which aggravate neuronal cell death. Nevertheless, the effect of PACAP on the cerebral circulation was not understood well. Therefore, in the present study, we determined the mean arterial blood pressure (MBP), regional cerebral blood flow (rCBF) and cerebral oxygen content (pO(2)) in mice, and estimated the therapeutically useful doses of PACAP. Under barbiturate anesthesia, polyethylene tubes were inserted into mice to monitor MBP and to administer PACAP (5x10(-13)-5x10(-8) mol/kg) or ***vasoactive intestinal peptide*** (VIP; 5x10(-12) and 5x10 (-9) mol/kg). Then, MBP, rCBF and cerebral pO(2) were simultaneously measured in the mice. PACAP (5x10(-10)- 5x10(-9) mol/kg) injections transiently decreased MBP, and cerebral pO(2). PACAP (5x10(-8) mol/kg) injections produced a long-lasting potent decline of MBP, rCBF and cerebral pO(2). Therefore, PACAP should be applied at low doses which do not influence the MBP and cerebral circulation to determine the therapeutically useful doses of PACAP for neuroprotection. 

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AB ***Pituitary adenylate cyclase activating polypeptide*** (PACAP) modulates neurotransmission in the central and peripheral nervous systems. In vitro and in vivo studies have shown the protective effects of PACAP against neuronal damage induced by ***ischemia*** and agonists of NMDA-type glutamate receptors. Here, we demonstrated that PACAP also protected against neuronal toxicity induced by β-amyloid (Aβ) peptide, aggregation of which is a causative factor for Alzheimer's disease. PACAP (10(-9)M) rescued 80% of decreased cell viability and 50% of elevated caspase-3 activity that resulted from exposure of PC12 cells to Aβ. PACAP was at least 10(4)-fold more effective than other neuropeptides including ***vasoactive intestinal peptide*** (VIP) and humanin, which correlated with the level of cAMP accumulation. Thus, our results suggested that PACAP attenuates Aβ-induced cell death in PC12 cells through an increase in cAMP and that caspase-3 deactivation by PACAP is involved in the signaling pathway for this neuroprotection. 

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AB Both ***vasoactive intestinal peptide*** (VIP) and ***pituitary adenylate cyclase-activating polypeptide*** (PACAP) act as neurotransmitters in the central and peripheral nervous systems. Attention has been focused on these neuropeptides because among their numerous biological activities, they have been confirmed to show neuroprotective effects against

***ischemia*** and glutamate-induced cytotoxicity. It is well established that glutamate has excitatory effects on neuronal cells, and that excessive glutamate shows potent neurotoxicity, especially in neuronal nitric oxide synthase-containing neurons. Glutamate stimulates the production of nitric oxide (NO) in neurons, and the NO generated is tightly associated with the delayed death of neurons. We examined the effects of these neuropeptides on the glutamate-induced neural actions using PC12 cells, and we confirmed the important activities of PACAP/VIP on the production of NO as well as the delayed cell death stimulated by glutamate. 

L25 ANSWER 32 OF 33 EMBASE 

AB ***Vasoactive intestinal peptide*** (VIP) is a neuropeptide synthesized by immune cells that can modulate several immune aspects, including the function of cells involved in the inflammatory response, such as macrophages and monocytes. The production and release of cytokines by activated phagocytes are important events in the pathogenesis of ***ischemia***-reperfusion injury. There is abundant evidence that the proinflammatory cytokine TNF-α is an important mediator of shock and organ failure complicating Gram-negative sepsis. VIP has been shown to attenuate the deleterious consequences of this pathologic phenomenon. In this study we have investigated the effects of VIP and the structurally related neuropeptide ***pituitary adenylate cyclase- activating polypeptide*** (PACAP38) on the production of TNF-α by endotoxin- activated murine peritoneal macrophages. Both neuropeptides rapidly and specifically inhibit the LPS-stimulated production of TNF-α, exerting their action through the binding to VPAC1 receptor and the subsequent activation of the adenylate cyclase system. VIP and PACAP regulate the production of TNF- α at a transcriptional level. In vitro results were correlated with an inhibition of both TNF-α expression and release in endotoxemic mice in vivo. The immunomodulatory role of VIP in vivo is supported by the up-regulation of VIP release in serum and peritoneal fluid by LPS and proinflammatory cytokines such as TNF-α, IL-1β, and IL-6. These findings support the idea that under toxicity conditions associated with high LPS doses, VIP and PACAP could act as protective mediators that regulate the excessive release of TNF- α to reduce inflammation or shock.

L25 ANSWER 33 OF 33 EMBASE 

AB ***Vasoactive intestinal peptide*** (VIP) is a neuropeptide synthesized by immune cells that can modulate several immune aspects, including the function of cells involved in the inflammatory response, such as macrophages and monocytes. Production and release of cytokines by activated mononuclear phagocytes is an important event in the pathogenesis of ***ischemia***-reperfusion injury. VIP has been shown to attenuate the deleterious consequences of this pathologic phenomenon. We have investigated the effects of VIP and PACAP38 on the production of interleukin-6 (IL-6), a proinflammatory cytokine, by endotoxin-activated murine macrophages. Both neuropeptides exhibit a dual effect on the IL-6 production by peritoneal macrophages. Whereas VIP and PACAP inhibit with similar dose-response curves the release of IL-6 from macrophages stimulated with a LPS dose range from 100 pg/mL to 10 μg/mL, both neuropeptides enhance IL-6 secretion in unstimulated macrophages and in macrophages stimulated with very low LPS concentrations (1-10 pg/mL). The inhibition on LPS-induced IL-6 production is specific, presumably mediated through a subtype of the PACAP-R. VIP and PACAP regulate the production of IL-6 at a transcriptional level. These results were correlated with an inhibition on both IL-6 expression and release in endotoxemic mice in vivo. These findings support the idea that in the absence of stimulation or in the presence of low doses of LPS, VIP and PACAP could play a role in immune system homeostasis. However, under toxicity conditions associated

with high LPS doses, VIP and PACAP could act as protective mediators that regulate the excessive release of IL-6 in order to reduce inflammation or shock.

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L26 248 L24 AND MUSCLE

=> s l26 and bronchial
L27 9 L26 AND BRONCHIAL

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L27 ANSWER 1 OF 9 MEDLINE on STN
AB Chronic inflammatory airway diseases such as ***bronchial*** asthma or chronic obstructive pulmonary disease (COPD) are major contributors to the global burden of disease. Although inflammatory cells play the central role in the pathogenesis of the diseases, recent observations indicate that also resident respiratory cells represent important targets for pulmonary drug development. Especially targeting airway neuromediators offers a possible mechanism by which respiratory diseases may be treated in the future. Among numerous peptide mediators such as tachykinins, calcitonin gene-related peptide, neurotrophins or opioids, vasoactive intestinal polypeptide (VIP) is one of the most abundant molecules found in the respiratory tract. In human airways, it influences many respiratory functions via the receptors VPAC1, VPAC2 and PAC1. VIP-expressing nerve fibers are present in the tracheobronchial smooth ***muscle*** layer, submucosal glands and in the walls of pulmonary and ***bronchial*** arteries and veins. Next to its strong bronchodilator effects, VIP potently relaxes pulmonary vessels, and plays a pivotal role in the mediation of immune mechanisms. A therapy utilizing the respiratory effects of VIP would offer potential benefits in the treatment of obstructive and inflammatory diseases and long acting VIP-based synthetic non-peptide compounds may represent a novel target for drug development.

L27 ANSWER 2 OF 9 MEDLINE on STN
AB Ro 25-1553 is a metabolically stable analogue of endogenous vasoactive intestinal polypeptide (VIP). This compound is a potent bronchodilator in vitro as well as in vivo. Moreover, Ro 25-1553 has been shown to be highly selective of the VPAC2 receptor. We assessed the effect of Ro 25-1553 on isolated human bronchi and pulmonary arteries in vitro. Macroscopically normal human airways and pulmonary arteries were obtained from patients undergoing surgery for lung cancer. The relaxing capability of Ro 25-1553 on ***bronchial*** and pulmonary artery tone was measured using standard techniques. ***Bronchial*** rings were pre-contracted with 0.1 mM histamine, and tone in pulmonary artery rings was induced with 10 microM PGF2alpha. Increasing concentrations of Ro 25-1553 within a range of 1 pM to 10 microM were added and isometric tension changes were recorded. Ro 25-1553 caused a concentration-dependent relaxation of airway and pulmonary artery preparations, with an EC50 of approximately 10 nM and a maximal relaxation of 70%-75% of the induced tone. The presence of VPAC2 receptors in the two tissues, though low in density, was confirmed by in situ hybridization, immunocytochemistry and ligand binding. These findings indicate that the VIP analogue Ro 25-1553 may be useful in the treatment of asthma and/or chronic obstructive pulmonary diseases.

L27 ANSWER 3 OF 9 MEDLINE on STN
AB Pituitary adenylate cyclase-activating peptide (PACAP) 38 displays several biological activities relevant to obstructive airway disease. In this study, the occurrence of PACAP 38 in human small bronchi and corresponding pulmonary arteries was analysed immunocytochemically. The dilatory effects of this peptide on the same structures were also studied in vitro.

A moderate number of PACAP-like immunoreactive nerve fibres was seen in association with ***bronchial*** and vascular smooth ***muscle*** and around seromucous glands. PACAP 38 caused a concentration-dependent relaxation of precontracted ***bronchial*** and pulmonary arterial segments. The maximal relaxation was more pronounced in the airways than in the arteries, whereas the potency in both was identical. PACAP 38 caused relaxation of all segments tested (nine patients), whereas vasoactive intestinal polypeptide (VIP) failed to cause relaxation of ***bronchial*** segments from six of nine patients. Both PACAP and VIP dilated all pulmonary arterial segments tested. In conclusion, pituitary adenylate cyclase-activating peptide 38 is a potent dilator of human bronchi and is present in the human lung. Pituitary adenylate cyclase-activating peptide 38 may, therefore, play a role in the endogenous regulation of airway tone. The inhibitory effects of pituitary adenylate cyclase-activating peptide 38 are more consistent than those of the related neuropeptide vasoactive intestinal polypeptide, perhaps reflecting a difference in susceptibility to degrading enzymes.

L27 ANSWER 4 OF 9 MEDLINE on STN

AB Pituitary adenylate cyclase-activating peptide (PACAP) is present in nerves in the vicinity of ***bronchial*** and vascular smooth ***muscle*** in the airways. At least one endogenous form of PACAP, PACAP 1-27, has high affinity binding sites in the lung, probably including cholinergic nerve terminals, ***bronchial*** smooth ***muscle***, epithelial and mononuclear inflammatory cells. The mechanism of action for PACAP 1-27 and 1-38 in vivo involves endogenous catecholamines, peptidases and nitric oxide, depending on tissue type. Intracellularly, cyclic adenosine monophosphate (cAMP) as well as calcium and sodium mobilization is probably involved. PACAP 1-27 and 1-38 inhibit airway smooth ***muscle*** tone in vitro and in vivo. The inhibitory effect of PACAP 1-38 is more sustained than that of PACAP 1-27, in vitro as well as in vivo. PACAP 1-38 also causes more sustained inhibition of bronchoconstriction after inhalation in vivo, than does ***vasoactive intestinal peptide*** (VIP). PACAP 1-27 given intravenously virtually abolishes allergen-induced bronchoconstriction in vivo. Novel synthetic analogues of PACAP 1-27 cause more sustained inhibition of airway smooth ***muscle*** tone in vitro and in vivo than do PACAP 1-27 or 1-38. Both PACAP 1-27 and 1-38 inhibit arterial smooth ***muscle*** tone but, administration of PACAP 1-27, 1-38 or a structural analogue of PACAP 1-27 in the airways, induces no cardiovascular side effects at doses inhibiting bronchoconstriction. PACAP 1-38 enhances phagocytosis in macrophages and inhibits the release of the pro-inflammatory cytokine interleukin-2 in lymphocytes, suggesting antiinflammatory effects. It is concluded that pituitary adenylate cyclase-activating peptide 1-27 and 1-38, or structurally related molecules, may be useful as bronchodilators but their effect on human ***bronchial*** smooth ***muscle*** and on human inflammatory cells is in need of evaluation.

L27 ANSWER 5 OF 9 MEDLINE on STN

AB Asthma is a chronic inflammatory disorder of the airways in which many cells participate. This inflammation causes recurrent episodes and symptoms that are associated with widespread but variable airflow limitation that is at least partly reversible either spontaneously or with treatment. Therefore, an investigation of useful remedies for the treatment of ***bronchial*** asthma is proposed. In this study, we determined whether both forms of ***pituitary adenylate cyclase activating polypeptide*** (PACAP 38 and PACAP 27) belonging to the ***vasoactive intestinal peptide*** (VIP) family of peptides could inhibit the effects of histamine-induced respiratory resistance (Rr) in anesthetized guinea pigs, when compared with VIP. The order for 50% suppression (ED50) of Rr induced by peptides was VIP > PACAP 27 > PACAP 38. The inhibitory effects induced by PACAP 38 on histamine-induced Rr in guinea pigs were more

prolonged than with the other two peptides. Moreover, adding the endopeptidase inhibitor phosphoramidon prolonged the inhibitory effects of PACAPs. These results suggested that the exogenous peptides of the inhibitory nonadrenergic noncholinergic nervous (i-NANC) peptides could become a useful remedy for treatment of ***bronchial*** asthma, because these belong to an important intrinsic hormone.

L27 ANSWER 6 OF 9 MEDLINE on STN
AB RO 25-1553 is a synthetic VIP analogue that induced a long-lasting relaxation of tracheal and ***bronchial*** smooth ***muscles*** as well as a reduction of edema and eosinophilic mobilization during pulmonary anaphylaxis. In the present study, we tested in vitro the capacity of RO 25-1553 to occupy the different VIP/PACAP receptor subclasses and to stimulate adenylate cyclase activity. The cellular models tested expressed one single receptor subtype: Chinese hamster ovary (CHO) cells transfected with the rat recombinant PACAP I, rat VIP1, and human VIP2 receptors; SUP T1 cells expressing the human VIP2 and HCT 15 and LoVo cells expressing the human VIP1 receptor. RO 25-1553 was threefold more potent than VIP on the human VIP2 receptor, 100- and 600-fold less potent than VIP on the rat and human VIP1 receptors, respectively, and 10-fold less potent than VIP and 3000-fold less potent than PACAP on the PACAP I receptor. RO 25-1553 was a full agonist on the VIP2, the PACAP I, and the rat recombinant VIP1 receptor but a partial agonist only on the human VIP1 receptor. Thus, RO 25-1553 is a highly selective agonist ligand for the VIP2 receptor subclass.

L27 ANSWER 7 OF 9 MEDLINE on STN
AB Pituitary adenylate cyclase-activating peptide (PACAP) is a ***vasoactive intestinal peptide*** (VIP)-like peptide recently isolated from ovine hypothalami. Nerve fibers displaying PACAP immunoreactivity were found in the respiratory tract of rats, guinea pigs, ferrets, pigs, sheep and squirrel monkeys. A moderate supply of PACAP-immunoreactive fibers was seen in the nasal mucosa of guinea pigs. Few to moderate numbers of PACAP-containing fibers occurred in the tracheo-***bronchial*** wall of rats, guinea pigs, ferrets, pigs, sheep and squirrel monkeys. The fibers were distributed beneath the epithelium, around blood vessels and seromucous glands, and among bundles of smooth ***muscle***. In the lungs, the immunoreactive fibers were observed close to small bronchioli. A few PACAP-immunoreactive nerve cell bodies were seen in the sphenopalatine and otic ganglia of guinea pigs. Simultaneous double immunostaining of the respiratory tract of sheep and ferrets revealed that all PACAP-containing nerve fibers stored VIP. We suggest that neuronal PACAP may take part in the regulation of smooth ***muscle*** tone and glandular secretion.

L27 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
AB To explore the role of intrapulmonary neuropeptides in the development of airway hyperresponsiveness, an animal model of airway hyperresponsiveness (AHR) was established in rabbits by using ozone exposure. With the model, after test of the mechanics of respiration and bronchoalveolar lavage assay, the levels of ***vasoactive intestinal peptide*** (VIP) and calcitonin gene-related peptide (CGRP) in the lungs were determined by RIA, and the expression of mRNA coding receptors of these two neuropeptides was evaluated by reverse transcriptional-polymerase chain reaction (RT-PCR). At the same time, the distribution of VIP receptor-1 (VIPR1) and CGRP receptor-1 (CGRPR1) in lung tissues and its time-course were examined by in situ hybridization. The results showed: in ozone-stressing groups, airway resistance increased significantly and typical inflammatory pathol. changes were observed in pulmonary tissue slides, including neutrophil and eosinophil infiltration, mucus exudation and ***bronchial*** epithelial cells (BECs) shedding; with elongation of ozone exposure, the levels of VIP and CGRP in the lungs increased at first, reaching the peak on days 2 to 4, then decreased slowly, and CGRP peaked somewhat earlier than VIP; mRNA expression of the two neuropeptide

receptors in the lungs changed in a similar manner like VIP and CGRP, but the high level of mRNA expression of VIPR1 lasted longer than that of CGRPR1. In situ hybridization for neuropeptide receptors demonstrated that, in unstressed control, VIPR1 and CGRPR1 pos. cells appeared in the airway epithelium, pulmonary interstitial and focal areas of airway and vascular smooth ***muscles***. With the elongation of ozone exposure, hybridization stained deeper and the majority of pos. cells were located around the vessels and bronchus except a few in the alveoli. At 8 days, only a small number of pos. cells were seen in the lungs. From the results, it is concluded that ozone-stressing can induce the development of ARR, in which VIP and CGRP may play important roles. That implies, through binding to CGRPR1, CGRP stimulates an early inflammation response which contributes in cleaning up of irritants, while VIP exerts a later dampening of pulmonary inflammation response. These two neuropeptides may play sequential and complementary roles in the development of AHR.

L27 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
AB The neuropeptide ***vasoactive intestinal peptide*** (VIP) exerts its actions through two structurally related G protein-coupled receptors (VPAC1 and VPAC2). ***Pituitary adenylate cyclase-activating polypeptide*** (PACAP) is also a potent agonist of VPAC1 and VPAC2 receptors as well as of a third, PACAP-specific receptor (PAC1). The authors report the distribution of the VPAC2 receptor in peripheral tissues of the mouse, determined by receptor autoradiog. using [125I]VIP and the selective VPAC2 receptor agonist [125I]Ro25-1553 in wild-type and VPAC2 receptor-null mice. In addition, displacement expts. with the VPAC2-selective agonist Ro25-1553 and the VPAC1-selective agonist [K15,R16,L27]VIP(1-7)/GRF(8-27) were performed using the universal radioligand [125I]VIP. The VPAC2 receptor is found predominantly in smooth ***muscle*** (in blood vessels and in the smooth ***muscle*** layers of the gastrointestinal and reproductive systems), the basal part of the mucosal epithelium in the colon, lung, the vasculature of the kidney, adrenal medulla, and retina. Unexpectedly, the receptor was also present in thyroid follicular cells and acinar cells of the pancreas, tissues that have not been found to express the receptor in other species, and in very large amts. in the lung. The authors' data suggest novel functions of the VPAC2 receptor and addnl. potential therapeutic uses of drugs acting at the receptor (including the treatment of erectile dysfunction), but the authors' results also indicate that caution should be exercised in using the mouse as an animal model for the evaluation of VIP analogs intended for diagnostic or therapeutic use in man.

=> d l27 1-9 all

L27 ANSWER 1 OF 9 MEDLINE on STN
AN 2006132760 MEDLINE
DN PubMed ID: 16473346
TI Novel concepts of neuropeptide-based drug therapy: vasoactive intestinal polypeptide and its receptors.
AU Groneberg David A; Rabe Klaus F; Fischer Axel
CS Department of Respiratory Medicine, Hannover Medical School, Hannover, Germany.. groneberg.david@mh-hannover.de
SO European journal of pharmacology, (2006 Mar 8) Vol. 533, No. 1-3, pp. 182-94. Electronic Publication: 2006-02-10. Ref: 71
Journal code: 1254354. ISSN: 0014-2999.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 200605
ED Entered STN: 8 Mar 2006

Last Updated on STN: 12 May 2006
Entered Medline: 11 May 2006

AB Chronic inflammatory airway diseases such as ***bronchial*** asthma or chronic obstructive pulmonary disease (COPD) are major contributors to the global burden of disease. Although inflammatory cells play the central role in the pathogenesis of the diseases, recent observations indicate that also resident respiratory cells represent important targets for pulmonary drug development. Especially targeting airway neuromediators offers a possible mechanism by which respiratory diseases may be treated in the future. Among numerous peptide mediators such as tachykinins, calcitonin gene-related peptide, neurotrophins or opioids, vasoactive intestinal polypeptide (VIP) is one of the most abundant molecules found in the respiratory tract. In human airways, it influences many respiratory functions via the receptors VPAC1, VPAC2 and PAC1. VIP-expressing nerve fibers are present in the tracheobronchial smooth ***muscle*** layer, submucosal glands and in the walls of pulmonary and ***bronchial*** arteries and veins. Next to its strong bronchodilator effects, VIP potently relaxes pulmonary vessels, and plays a pivotal role in the mediation of immune mechanisms. A therapy utilizing the respiratory effects of VIP would offer potential benefits in the treatment of obstructive and inflammatory diseases and long acting VIP-based synthetic non-peptide compounds may represent a novel target for drug development.

CT Animals
Asthma: DT, drug therapy
Asthma: ME, metabolism
Bronchodilator Agents: ME, metabolism
Bronchodilator Agents: PD, pharmacology
*Bronchodilator Agents: TU, therapeutic use
Humans
Lung: BS, blood supply
Lung: DE, drug effects
Lung: IR, innervation
Lung: ME, metabolism
Mucus: SE, secretion
Neuropeptides: ME, metabolism
Neuropeptides: PD, pharmacology
Neuropeptides: TU, therapeutic use
***Pituitary Adenylate Cyclase-Activating Polypeptide: ME, metabolism***
Protein Conformation
Randomized Controlled Trials
***Receptors, Vasoactive Intestinal Peptide: CH, chemistry***
***Receptors, Vasoactive Intestinal Peptide: DE, drug effects***
***Receptors, Vasoactive Intestinal Peptide: ME, metabolism***
Research Support, Non-U.S. Gov't
Respiratory Mucosa: DE, drug effects
Respiratory Mucosa: ME, metabolism
T-Lymphocytes: DE, drug effects
T-Lymphocytes: ME, metabolism
Vagus Nerve: ME, metabolism
***Vasoactive Intestinal Peptide: ME, metabolism***
***Vasoactive Intestinal Peptide: PD, pharmacology***
***Vasoactive Intestinal Peptide: TU, therapeutic use***
*Vasodilation

RN ***37221-79-7 (Vasoactive Intestinal Peptide)***
CN 0 (Bronchodilator Agents); 0 (Neuropeptides); 0 (***Pituitary Adenylate Cyclase-Activating Polypeptide***); 0 (Receptors, ***Vasoactive Intestinal Peptide***)

L27 ANSWER 2 OF 9 MEDLINE on STN
AN 2001609068 MEDLINE
DN PubMed ID: 11683518

TI The effect of the vasoactive intestinal polypeptide agonist Ro 25-1553 on induced tone in isolated human airways and pulmonary artery.

AU Schmidt D T; Ruhlmann E; Waldeck B; Branscheid D; Luts A; Sundler F; Rabe K F

CS Leiden University Medical Centre, Department of Pulmonology, Leiden, The Netherlands.. D.Schmidt@lumc.nl

SO Naunyn-Schmiedeberg's archives of pharmacology, (2001 Oct) Vol. 364, No. 4, pp. 314-20.
Journal code: 0326264. ISSN: 0028-1298.

CY Germany: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200204

ED Entered STN: 2 Nov 2001
Last Updated on STN: 3 Apr 2002
Entered Medline: 1 Apr 2002

AB Ro 25-1553 is a metabolically stable analogue of endogenous vasoactive intestinal polypeptide (VIP). This compound is a potent bronchodilator in vitro as well as in vivo. Moreover, Ro 25-1553 has been shown to be highly selective of the VPAC2 receptor. We assessed the effect of Ro 25-1553 on isolated human bronchi and pulmonary arteries in vitro. Macroscopically normal human airways and pulmonary arteries were obtained from patients undergoing surgery for lung cancer. The relaxing capability of Ro 25-1553 on ***bronchial*** and pulmonary artery tone was measured using standard techniques. ***Bronchial*** rings were pre-contracted with 0.1 mM histamine, and tone in pulmonary artery rings was induced with 10 microM PGF2alpha. Increasing concentrations of Ro 25-1553 within a range of 1 pM to 10 microM were added and isometric tension changes were recorded. Ro 25-1553 caused a concentration-dependent relaxation of airway and pulmonary artery preparations, with an EC50 of approximately 10 nM and a maximal relaxation of 70%-75% of the induced tone. The presence of VPAC2 receptors in the two tissues, though low in density, was confirmed by in situ hybridization, immunocytochemistry and ligand binding. These findings indicate that the VIP analogue Ro 25-1553 may be useful in the treatment of asthma and/or chronic obstructive pulmonary diseases.

CT *Bronchi: DE, drug effects
Humans
Immunohistochemistry
In Situ Hybridization
In Vitro
Isometric Contraction: DE, drug effects
Lung: ME, metabolism
***Muscle Tonus: DE, drug effects***
****Muscle, Smooth: DE, drug effects***
****Muscle, Smooth, Vascular: DE, drug effects***
Neuropeptides: PD, pharmacology
*Peptides, Cyclic: PD, pharmacology
***Pituitary Adenylate Cyclase-Activating Polypeptide***
*Pulmonary Artery: DE, drug effects
Radioligand Assay
****Receptors, Vasoactive Intestinal Peptide: AG, agonists***
***Receptors, Vasoactive Intestinal Peptide: ME, metabolism***
***Receptors, Vasoactive Intestinal Peptide, Type II***
Tissue Distribution
****Vasoactive Intestinal Peptide: AG, agonists***
****Vasoactive Intestinal Peptide: AA, analogs & derivatives***
****Vasoactive Intestinal Peptide: PD, pharmacology***

RN ***37221-79-7 (Vasoactive Intestinal Peptide)***

CN 0 (ADCYAP1 protein, human); 0 (Neuropeptides); 0 (Peptides, Cyclic); 0 (***Pituitary Adenylate Cyclase-Activating Polypeptide***); 0 (Receptors, ***Vasoactive Intestinal Peptide***); 0 (Receptors, ***Vasoactive***

***Intestinal Peptide***, Type II); 0 (Ro 25-1553)

L27 ANSWER 3 OF 9 MEDLINE on STN
AN 2000169003 MEDLINE
DN PubMed ID: 10706486
TI Pituitary adenylate cyclase-activating peptide 38 a potent endogenously produced dilator of human airways.
AU Kinhult J; Andersson J A; Uddman R; Stjarne P; Cardell L O
CS Dept of Otorhinolaryngology, Malmo General Hospital, Sweden.
SO The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology, (2000 Feb) Vol. 15, No. 2, pp. 243-7.
Journal code: 8803460. ISSN: 0903-1936.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200003
ED Entered STN: 7 Apr 2000
Last Updated on STN: 7 Apr 2000
Entered Medline: 28 Mar 2000
AB Pituitary adenylate cyclase-activating peptide (PACAP) 38 displays several biological activities relevant to obstructive airway disease. In this study, the occurrence of PACAP 38 in human small bronchi and corresponding pulmonary arteries was analysed immunocytochemically. The dilatory effects of this peptide on the same structures were also studied in vitro. A moderate number of PACAP-like immunoreactive nerve fibres was seen in association with ***bronchial*** and vascular smooth ***muscle*** and around seromucous glands. PACAP 38 caused a concentration-dependent relaxation of precontracted ***bronchial*** and pulmonary arterial segments. The maximal relaxation was more pronounced in the airways than in the arteries, whereas the potency in both was identical. PACAP 38 caused relaxation of all segments tested (nine patients), whereas vasoactive intestinal polypeptide (VIP) failed to cause relaxation of ***bronchial*** segments from six of nine patients. Both PACAP and VIP dilated all pulmonary arterial segments tested. In conclusion, pituitary adenylate cyclase-activating peptide 38 is a potent dilator of human bronchi and is present in the human lung. Pituitary adenylate cyclase-activating peptide 38 may, therefore, play a role in the endogenous regulation of airway tone. The inhibitory effects of pituitary adenylate cyclase-activating peptide 38 are more consistent than those of the related neuropeptide vasoactive intestinal polypeptide, perhaps reflecting a difference in susceptibility to degrading enzymes.
CT Aged
Bronchi: IR, innervation
Bronchi: ME, metabolism
*Bronchodilator Agents: PD, pharmacology
Humans
In Vitro
Middle Aged
Nerve Fibers: CH, chemistry
Neuropeptides: ME, metabolism
*Neuropeptides: PD, pharmacology
Neurotransmitter Agents: ME, metabolism
*Neurotransmitter Agents: PD, pharmacology
***Pituitary Adenylate Cyclase-Activating Polypeptide***
Pulmonary Artery: IR, innervation
Pulmonary Artery: ME, metabolism
Research Support, Non-U.S. Gov't
***Vasoactive Intestinal Peptide: PD, pharmacology***
RN ***37221-79-7 (Vasoactive Intestinal Peptide)***
CN 0 (ADCYAP1 protein, human); 0 (Bronchodilator Agents); 0 (Neuropeptides); 0 (Neurotransmitter Agents); 0 (***Pituitary Adenylate Cyclase-Activating Polypeptide***)

L27 ANSWER 4 OF 9 MEDLINE on STN
AN 1999443451 MEDLINE
DN PubMed ID: 10515428
TI Bronchodilation by pituitary adenylate cyclase-activating peptide and related peptides.
AU Linden A; Cardell L O; Yoshihara S; Nadel J A
CS Lung Pharmacology Group, Dept of Respiratory Medicine & Allergology, Goteborg University, Gothenburg, Sweden.
SO The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology, (1999 Aug) Vol. 14, No. 2, pp. 443-51. Ref: 57
Journal code: 8803460. ISSN: 0903-1936.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 199911
ED Entered STN: 11 Jan 2000
Last Updated on STN: 11 Jan 2000
Entered Medline: 19 Nov 1999
AB Pituitary adenylate cyclase-activating peptide (PACAP) is present in nerves in the vicinity of ***bronchial*** and vascular smooth ***muscle*** in the airways. At least one endogenous form of PACAP, PACAP 1-27, has high affinity binding sites in the lung, probably including cholinergic nerve terminals, ***bronchial*** smooth ***muscle***, epithelial and mononuclear inflammatory cells. The mechanism of action for PACAP 1-27 and 1-38 in vivo involves endogenous catecholamines, peptidases and nitric oxide, depending on tissue type. Intracellularly, cyclic adenosine monophosphate (cAMP) as well as calcium and sodium mobilization is probably involved. PACAP 1-27 and 1-38 inhibit airway smooth ***muscle*** tone in vitro and in vivo. The inhibitory effect of PACAP 1-38 is more sustained than that of PACAP 1-27, in vitro as well as in vivo. PACAP 1-38 also causes more sustained inhibition of bronchoconstriction after inhalation in vivo, than does ***vasoactive intestinal peptide*** (VIP). PACAP 1-27 given intravenously virtually abolishes allergen-induced bronchoconstriction in vivo. Novel synthetic analogues of PACAP 1-27 cause more sustained inhibition of airway smooth ***muscle*** tone in vitro and in vivo than do PACAP 1-27 or 1-38. Both PACAP 1-27 and 1-38 inhibit arterial smooth ***muscle*** tone but, administration of PACAP 1-27, 1-38 or a structural analogue of PACAP 1-27 in the airways, induces no cardiovascular side effects at doses inhibiting bronchoconstriction. PACAP 1-38 enhances phagocytosis in macrophages and inhibits the release of the pro-inflammatory cytokine interleukin-2 in lymphocytes, suggesting antiinflammatory effects. It is concluded that pituitary adenylate cyclase-activating peptide 1-27 and 1-38, or structurally related molecules, may be useful as bronchodilators but their effect on human ***bronchial*** smooth ***muscle*** and on human inflammatory cells is in need of evaluation.
CT *Airway Resistance: PH, physiology
*Bronchi: IR, innervation
*Bronchoconstriction: PH, physiology
Endopeptidases: PH, physiology
Hemodynamic Processes: PH, physiology
Humans
Immunity, Cellular: PH, physiology
***Muscle Tonus: PH, physiology***
****Muscle, Smooth: IR, innervation***
*Neuropeptides: PH, physiology
*Neurotransmitter Agents: PH, physiology
*Peptide Fragments: PH, physiology
***Pituitary Adenylate Cyclase-Activating Polypeptide***

CN 0 (ADCYAP1 protein, human); 0 (Neuropeptides); 0 (Neurotransmitter Agents); 0 (Peptide Fragments); 0 (***Pituitary Adenylate Cyclase-Activating Polypeptide***); 0 (pituitary adenylate cyclase-activating-peptide (1-38), pig); EC 3.4.- (Endopeptidases)

L27 ANSWER 5 OF 9 MEDLINE on STN
AN 97392344 MEDLINE
DN PubMed ID: 9250576
TI Inhibitory effects of ***pituitary adenylate cyclase activating polypeptide*** on histamine-induced respiratory resistance in anesthetized guinea pigs.
AU Saguchi Y; Ando T; Watanabe T; Yamaki K; Suzuki R; Takagi K
CS Second Department of Internal Medicine, Nagoya University School of Medicine, Japan.
SO Regulatory peptides, (1997 May 14) Vol. 70, No. 1, pp. 9-13. Journal code: 8100479. ISSN: 0167-0115.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199709
ED Entered STN: 26 Sep 1997
Last Updated on STN: 26 Sep 1997
Entered Medline: 16 Sep 1997
AB Asthma is a chronic inflammatory disorder of the airways in which many cells participate. This inflammation causes recurrent episodes and symptoms that are associated with widespread but variable airflow limitation that is at least partly reversible either spontaneously or with treatment. Therefore, an investigation of useful remedies for the treatment of ***bronchial*** asthma is proposed. In this study, we determined whether both forms of ***pituitary adenylate cyclase activating polypeptide*** (PACAP 38 and PACAP 27) belonging to the ***vasoactive intestinal peptide*** (VIP) family of peptides could inhibit the effects of histamine-induced respiratory resistance (Rr) in anesthetized guinea pigs, when compared with VIP. The order for 50% suppression (ED50) of Rr induced by peptides was VIP > PACAP 27 > PACAP 38. The inhibitory effects induced by PACAP 38 on histamine-induced Rr in guinea pigs were more prolonged than with the other two peptides. Moreover, adding the endopeptidase inhibitor phosphoramidon prolonged the inhibitory effects of PACAPs. These results suggested that the exogenous peptides of the inhibitory nonadrenergic noncholinergic nervous (i-NANC) peptides could become a useful remedy for treatment of ***bronchial*** asthma, because these belong to an important intrinsic hormone.
CT Check Tags: Male
Airway Resistance
Animals
*Asthma: DT, drug therapy
*Bronchoconstriction: DE, drug effects
*Bronchodilator Agents: PD, pharmacology
Dose-Response Relationship, Drug
Drug Evaluation, Preclinical
Guinea Pigs
***Muscle Contraction: DE, drug effects***
***Muscle, Smooth: DE, drug effects***
*Neuropeptides: PD, pharmacology
Neuropeptides: TU, therapeutic use
***Pituitary Adenylate Cyclase-Activating Polypeptide***
Research Support, Non-U.S. Gov't
Time Factors
*Trachea: DE, drug effects
***Vasoactive Intestinal Peptide: PD, pharmacology***
RN ***37221-79-7 (Vasoactive Intestinal Peptide)***

CN 0 (Bronchodilator Agents); 0 (Neuropeptides); 0 (***Pituitary Adenylate Cyclase-Activating Polypeptide***)

L27 ANSWER 6 OF 9 MEDLINE on STN
AN 97290782 MEDLINE
DN PubMed ID: 9145428
TI The long-acting vasoactive intestinal polypeptide agonist RO 25-1553 is highly selective of the VIP2 receptor subclass.
AU Gourlet P; Vertongen P; Vandermeers A; Vandermeers-Piret M C; Rathe J; De Neef P; Waelbroeck M; Robberecht P
CS Department of Biochemistry and Nutrition, Medical School, Universite Libre de Bruxelles, Brussels, Belgium.
SO Peptides, (1997) Vol. 18, No. 3, pp. 403-8.
Journal code: 8008690. ISSN: 0196-9781.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199707
ED Entered STN: 24 Jul 1997
Last Updated on STN: 6 Feb 1998
Entered Medline: 17 Jul 1997
AB RO 25-1553 is a synthetic VIP analogue that induced a long-lasting relaxation of tracheal and ***bronchial*** smooth ***muscles*** as well as a reduction of edema and eosinophilic mobilization during pulmonary anaphylaxis. In the present study, we tested in vitro the capacity of RO 25-1553 to occupy the different VIP/PACAP receptor subclasses and to stimulate adenylate cyclase activity. The cellular models tested expressed one single receptor subtype: Chinese hamster ovary (CHO) cells transfected with the rat recombinant PACAP I, rat VIP1, and human VIP2 receptors; SUP T1 cells expressing the human VIP2 and HCT 15 and LoVo cells expressing the human VIP1 receptor. RO 25-1553 was threefold more potent than VIP on the human VIP2 receptor, 100- and 600-fold less potent than VIP on the rat and human VIP1 receptors, respectively, and 10-fold less potent than VIP and 3000-fold less potent than PACAP on the PACAP I receptor. RO 25-1553 was a full agonist on the VIP2, the PACAP I, and the rat recombinant VIP1 receptor but a partial agonist only on the human VIP1 receptor. Thus, RO 25-1553 is a highly selective agonist ligand for the VIP2 receptor subclass.
CT Adenylate Cyclase: ME, metabolism
Amino Acid Sequence
Animals
CHO Cells
Cricetinae
Enzyme Activation: DE, drug effects
Humans
Molecular Sequence Data
Neuropeptides: CS, chemical synthesis
Neuropeptides: PD, pharmacology
Peptides, Cyclic: AG, agonists
*Peptides, Cyclic: PD, pharmacology
***Pituitary Adenylate Cyclase-Activating Polypeptide***
Rats
***Receptors, Pituitary Adenylate Cyclase-Activating Polypeptide***
Receptors, Pituitary Hormone: DE, drug effects
***Receptors, Vasoactive Intestinal Peptide: CH, chemistry***
****Receptors, Vasoactive Intestinal Peptide: DE, drug effects***
****Receptors, Vasoactive Intestinal Peptide: ME, metabolism***
***Receptors, Vasoactive Intestinal Peptide, Type II***
Receptors, Vasoactive Intestinal Polypeptide, Type I
Recombinant Proteins
Research Support, Non-U.S. Gov't
Transfection

Tumor Cells, Cultured
***Vasoactive Intestinal Peptide: AG, agonists***
****Vasoactive Intestinal Peptide: AA, analogs & derivatives***
***Vasoactive Intestinal Peptide: PD, pharmacology***
RN ***37221-79-7 (Vasoactive Intestinal Peptide)***
CN 0 (ADCYAP1 protein, human); 0 (Adcyap1 protein, rat); 0 (Neuropeptides); 0 (Peptides, Cyclic); 0 (***Pituitary Adenylate Cyclase-Activating Polypeptide***); 0 (Receptors, ***Pituitary Adenylate Cyclase-Activating Polypeptide***); 0 (Receptors, Pituitary Hormone); 0 (Receptors, ***Vasoactive Intestinal Peptide***); 0 (Receptors, ***Vasoactive Intestinal Peptide***, Type II); 0 (Receptors, Vasoactive Intestinal Polypeptide, Type I); 0 (Recombinant Proteins); 0 (Ro 25-1553); EC 4.6.1.1 (Adenylate Cyclase)

L27 ANSWER 7 OF 9 MEDLINE on STN
AN 92005632 MEDLINE
DN PubMed ID: 1913779
TI Pituitary adenylate cyclase-activating peptide (PACAP), a new ***vasoactive intestinal peptide*** (VIP)-like peptide in the respiratory tract.
AU Uddman R; Luts A; Arimura A; Sundler F
CS Department of Otorhinolaryngology, Malmo General Hospital, Sweden.
SO Cell and tissue research, (1991 Jul) Vol. 265, No. 1, pp. 197-201. Journal code: 0417625. ISSN: 0302-766X.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199110
ED Entered STN: 24 Jan 1992
Last Updated on STN: 29 Jan 1996
Entered Medline: 30 Oct 1991
AB Pituitary adenylate cyclase-activating peptide (PACAP) is a ***vasoactive intestinal peptide*** (VIP)-like peptide recently isolated from ovine hypothalami. Nerve fibers displaying PACAP immunoreactivity were found in the respiratory tract of rats, guinea pigs, ferrets, pigs, sheep and squirrel monkeys. A moderate supply of PACAP-immunoreactive fibers was seen in the nasal mucosa of guinea pigs. Few to moderate numbers of PACAP-containing fibers occurred in the tracheo-***bronchial*** wall of rats, guinea pigs, ferrets, pigs, sheep and squirrel monkeys. The fibers were distributed beneath the epithelium, around blood vessels and seromucous glands, and among bundles of smooth ***muscle***. In the lungs, the immunoreactive fibers were observed close to small bronchioli. A few PACAP-immunoreactive nerve cell bodies were seen in the sphenopalatine and otic ganglia of guinea pigs. Simultaneous double immunostaining of the respiratory tract of sheep and ferrets revealed that all PACAP-containing nerve fibers stored VIP. We suggest that neuronal PACAP may take part in the regulation of smooth ***muscle*** tone and glandular secretion.
CT Animals
Bronchi: CY, cytology
Bronchi: IM, immunology
Bronchi: IR, innervation
Ferrets
Fluorescent Antibody Technique
Guinea Pigs
Immune Sera: IM, immunology
Immunohistochemistry
Lung: CY, cytology
Lung: IM, immunology
Lung: IR, innervation
Nasal Mucosa: CY, cytology
Nasal Mucosa: IM, immunology

Nasal Mucosa: IR, innervation
Nerve Fibers: IM, immunology
Nerve Fibers: UL, ultrastructure
*Neuropeptides: AN, analysis
Neuropeptides: IM, immunology
***Pituitary Adenylate Cyclase-Activating Polypeptide***
Rats
Research Support, Non-U.S. Gov't
*Respiratory System: CH, chemistry
Respiratory System: IM, immunology
Respiratory System: IR, innervation
Saimiri
Sheep
Swine
Trachea: CY, cytology
Trachea: IM, immunology
Trachea: IR, innervation
***Vasoactive Intestinal Peptide: AN, analysis***
***Vasoactive Intestinal Peptide: IM, immunology***
RN ***37221-79-7 (Vasoactive Intestinal Peptide)***
CN 0 (Adcyap1 protein, rat); 0 (Immune Sera); 0 (Neuropeptides); 0 (***Pituitary Adenylate Cyclase-Activating Polypeptide***)

L27 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2005:435243 CAPLUS
DN 144:20800
ED Entered STN: 24 May 2005
TI Temporal and spatial distribution of VIP, CGRP and their receptors in the development of airway hyperresponsiveness in the lungs
AU Ren, Yanhong; Qin, Xiaoqun; Guan, Chaxiang; Luo, Ziqiang; Zhang, Changqing; Sun, Xiuhong
CS Xiangya Medical School, Central South University, Changsha, 410078, Peop. Rep. China
SO Shengli Xuebao (2004), 56(2), 137-146
CODEN: SLHPAH; ISSN: 0371-0874
PB Kexue Chubanshe
DT Journal
LA English
CC 14-4 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 2, 4
AB To explore the role of intrapulmonary neuropeptides in the development of airway hyperresponsiveness, an animal model of airway hyperresponsiveness (AHR) was established in rabbits by using ozone exposure. With the model, after test of the mechanics of respiration and bronchoalveolar lavage assay, the levels of ***vasoactive intestinal peptide*** (VIP) and calcitonin gene-related peptide (CGRP) in the lungs were determined by RIA, and the expression of mRNA coding receptors of these two neuropeptides was evaluated by reverse transcriptional-polymerase chain reaction (RT-PCR). At the same time, the distribution of VIP receptor-1 (VIPR1) and CGRP receptor-1 (CGRPR1) in lung tissues and its time-course were examined by in situ hybridization. The results showed: in ozone-stressing groups, airway resistance increased significantly and typical inflammatory pathol. changes were observed in pulmonary tissue slides, including neutrophil and eosinophil infiltration, mucus exudation and ***bronchial*** epithelial cells (BECs) shedding; with elongation of ozone exposure, the levels of VIP and CGRP in the lungs increased at first, reaching the peak on days 2 to 4, then decreased slowly, and CGRP peaked somewhat earlier than VIP; mRNA expression of the two neuropeptide receptors in the lungs changed in a similar manner like VIP and CGRP, but the high level of mRNA expression of VIPR1 lasted longer than that of CGRPR1. In situ hybridization for neuropeptide receptors demonstrated that, in unstressed control, VIPR1 and CGRPR1 pos. cells appeared in the airway epithelium, pulmonary interstitial and focal areas of airway and

vascular smooth ***muscles***. With the elongation of ozone exposure, hybridization stained deeper and the majority of pos. cells were located around the vessels and bronchus except a few in the alveoli. At 8 days, only a small number of pos. cells were seen in the lungs. From the results, it is concluded that ozone-stressing can induce the development of ARR, in which VIP and CGRP may play important roles. That implies, through binding to CGRPR1, CGRP stimulates an early inflammation response which contributes in cleaning up of irritants, while VIP exerts a later dampening of pulmonary inflammation response. These two neuropeptides may play sequential and complementary roles in the development of AHR.

ST airway hyperresponsiveness bronchi epithelium VIP CGRP ozone

IT VIP receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(VIP1; temporal and spatial distribution of VIP, CGRP and their receptors in development of airway hyperresponsiveness in lungs)

IT Epithelium
(***bronchial***; temporal and spatial distribution of VIP, CGRP and their receptors in development of airway hyperresponsiveness in lungs)

IT Bronchi
(epithelium; temporal and spatial distribution of VIP, CGRP and their receptors in development of airway hyperresponsiveness in lungs)

IT Respiratory system, disease
(hyperresponsiveness; temporal and spatial distribution of VIP, CGRP and their receptors in development of airway hyperresponsiveness in lungs)

IT Inflammation
Lung, disease
(pneumonitis; temporal and spatial distribution of VIP, CGRP and their receptors in development of airway hyperresponsiveness in lungs)

IT Disease models
Lung
Oryctolagus cuniculus
(temporal and spatial distribution of VIP, CGRP and their receptors in development of airway hyperresponsiveness in lungs)

IT Calcitonin gene-related peptide receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type CGRP1; temporal and spatial distribution of VIP, CGRP and their receptors in development of airway hyperresponsiveness in lungs)

IT ***Pituitary adenylate cyclase-activating polypeptide*** receptor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type II; temporal and spatial distribution of VIP, CGRP and their receptors in development of airway hyperresponsiveness in lungs)

IT 10028-15-6, Ozone, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(temporal and spatial distribution of VIP, CGRP and their receptors in development of airway hyperresponsiveness in lungs)

IT 37221-79-7, ***Vasoactive intestinal peptide***
83652-28-2, Calcitonin gene-related peptide
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(temporal and spatial distribution of VIP, CGRP and their receptors in development of airway hyperresponsiveness in lungs)

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE


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L27 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:161133 CAPLUS
DN 140:297855
ED Entered STN: 27 Feb 2004
TI Distribution of the VPAC2 receptor in peripheral tissues of the mouse
AU Harmar, Anthony J.; Sheward, W. John; Morrison, Christine F.; Waser, Beatrice; Gugger, Mathias; Reubi, Jean Claude
CS Division of Neuroscience, School of Biomedical and Clinical Laboratory Sciences, University of Edinburgh, Edinburgh, EH8 9JZ, UK
SO Endocrinology (2004), 145(3), 1203-1210
CODEN: ENDOAO; ISSN: 0013-7227
PB Endocrine Society
DT Journal
LA English
CC 2-6 (Mammalian Hormones)
AB The neuropeptide ***vasoactive intestinal peptide*** (VIP) exerts its actions through two structurally related G protein-coupled receptors (VPAC1 and VPAC2). ***Pituitary adenylate cyclase-activating polypeptide*** (PACAP) is also a potent agonist of VPAC1 and VPAC2 receptors as well as of a third, PACAP-specific receptor (PAC1). The authors report the distribution of the VPAC2 receptor in peripheral tissues of the mouse, determined by receptor autoradiog. using [125I]VIP and the selective VPAC2 receptor agonist [125I]Ro25-1553 in wild-type and VPAC2 receptor-null mice. In addition, displacement expts. with the VPAC2-selective agonist Ro25-1553 and the VPAC1-selective agonist [K15,R16,L27]VIP(1-7)/GRF(8-27) were performed using the universal radioligand [125I]VIP. The VPAC2 receptor is found predominantly in smooth ***muscle*** (in blood vessels and in the smooth ***muscle*** layers of the gastrointestinal and reproductive systems), the basal part of the mucosal epithelium in the colon, lung, the vasculature of the kidney, adrenal medulla, and retina. Unexpectedly, the receptor was also present in thyroid follicular cells and acinar cells of the pancreas, tissues that have not been found to express the receptor in other species, and in very large amts. in the lung. The authors' data suggest novel functions of the VPAC2 receptor and addnl. potential therapeutic uses of drugs acting at the receptor (including the treatment of erectile

dysfunction), but the authors' results also indicate that caution should be exercised in using the mouse as an animal model for the evaluation of VIP analogs intended for diagnostic or therapeutic use in man.

ST VPAC2 receptor expression peripheral tissue smooth ***muscle*** mucosa mouse

IT Testis
(Leydig cell; distribution of VPAC2 receptor in peripheral tissues of mouse)

IT VIP receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(VIP1; distribution of VPAC2 receptor in peripheral tissues of mouse)

IT VIP receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(VIP2; distribution of VPAC2 receptor in peripheral tissues of mouse)

IT Pancreas
(acinar cell; distribution of VPAC2 receptor in peripheral tissues of mouse)

IT Lung
(alveolus; distribution of VPAC2 receptor in peripheral tissues of mouse)

IT Epithelium
(***bronchial***; distribution of VPAC2 receptor in peripheral tissues of mouse)

IT Adrenal gland
(capsule; distribution of VPAC2 receptor in peripheral tissues of mouse)

IT Intestine
(colon, mucosa; distribution of VPAC2 receptor in peripheral tissues of mouse)

IT Penis
(corpus cavernosum; distribution of VPAC2 receptor in peripheral tissues of mouse)

IT Kidney
Thymus gland
(cortex; distribution of VPAC2 receptor in peripheral tissues of mouse)

IT Adipose tissue
Adrenal medulla
Bladder
Cardiovascular system
Digestive tract
Epididymis
Esophagus
Gallbladder
Heart
Liver
***Muscle***
Oviduct
Reproductive system
Vas deferens
(distribution of VPAC2 receptor in peripheral tissues of mouse)

IT Intestine
(duodenum, mucosa; distribution of VPAC2 receptor in peripheral tissues of mouse)

IT Bronchi
Mucous membrane
Prostate gland
Trachea (anatomical)
(epithelium; distribution of VPAC2 receptor in peripheral tissues of mouse)

IT Thyroid gland
(follicle; distribution of VPAC2 receptor in peripheral tissues of mouse)

IT Uterus
(gland; distribution of VPAC2 receptor in peripheral tissues of mouse)

IT Intestine
(ileum, mucosa; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT Intestine
(jejunum, mucosa; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT Lymphocyte
(lymph node; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT Lymph node
(lymphocyte; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT Thymus gland
(medulla; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT Stomach
(mucosa; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT Epithelium
(mucosal; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT Mucous membrane
(muscularis; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT Animal tissue
(peripheral; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT Epithelium
(prostatic; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT Intestine
(rectum, mucosa; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT Eye
(retina; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT Blood vessel
(smooth ***muscle***; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT ***Muscle***
(smooth; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT Epithelium
(tracheal; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT Testis
(tunica albuginea; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT ***Pituitary adenylate cyclase-activating polypeptide*** receptor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type II; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT ***Pituitary adenylate cyclase-activating polypeptide*** receptor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type III; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT Gland
(uterine; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT Spleen
(white pulp; distribution of VPAC2 receptor in peripheral tissues of mouse)
IT 37221-79-7, ***Vasoactive intestinal peptide***
159427-08-4, Ro25-1553 201995-58-6
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(distribution of VPAC2 receptor in peripheral tissues of mouse)
RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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=> s l24 and cerebrovascular(w)disorder
L28 2 L24 AND CEREBROVASCULAR(W) DISORDER

=> d l28 1-2 all

L28 ANSWER 1 OF 2 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2006:624548 BIOSIS
DN PREV200600644019
TI Novel PACAP analogs that selectively bind to PACAP-I receptor.
AU Dong, Jesse Z. [Reprint Author]; Shen, Yeelana; Taylor, John E.; Culler, Michael; Moreau, Jacques-Pierre
CS Biomeasure Incorp, IPSEN Grp, 27 Maple St, Milford, MA 01757 USA
SO Chorev, M [Editor]; Sawyer, TK [Editor]. (2004) pp. 700-701. Peptide Revolution: Genomics, Proteomics & Therapeutics.
Publisher: AMER CHEMICAL SOC, 1155 SIXTEENTH ST NW, WASHINGTON, DC 20036 USA.

Meeting Info.: 18th American Peptide Symposium. BOSTON, MA, USA. July 19 -23, 2003.
ISBN: 0-9715560-1-6(H).
DT Book; (Book Chapter)
Conference; (Meeting)
LA English
ED Entered STN: 22 Nov 2006
Last Updated on STN: 22 Nov 2006
CC Biochemistry studies - Proteins, peptides and amino acids 10064
Pathology - Therapy 12512
Cardiovascular system - Physiology and biochemistry 14504
Cardiovascular system - Blood vessel pathology 14508
Nervous system - Physiology and biochemistry 20504
Nervous system - Pathology 20506
Pharmacology - General 22002
Pharmacology - Neuropharmacology 22024
IT Major Concepts
Pharmacology; Cardiovascular System (Transport and Circulation); Nervous System (Neural Coordination)
IT Diseases
stroke: vascular disease, nervous system disease
***Cerebrovascular Disorders*** (MeSH)
IT Diseases
brain damage: nervous system disease, injury
IT Chemicals & Biochemicals
glucagon; ***vasoactive intestinal peptide*** [VIP]; secretin; ***pituitary adenylate cyclase-activating polypeptide*** 27 [PACAP27]; ***pituitary adenylate cyclase-activating polypeptide***-II receptor [PACAP-IIR]; ***pituitary adenylate cyclase-activating polypeptide*** 38 [PACAP38]: neuroprotectant-drug; ***pituitary adenylate cyclase-activating polypeptide***-I receptor [PACAP-I receptor]: neuroprotectant-drug
ORGN Classifier
Animalia 33000
Super Taxa
Animalia
Organism Name
animal (common)
Taxa Notes
Animals
RN 9007-92-5 (glucagon)
37221-79-7 (***vasoactive intestinal peptide***)
37221-79-7 (VIP)
1393-25-5 (secretin)
129069-75-6 (***pituitary adenylate cyclase-activating polypeptide*** 27)
129069-75-6 (PACAP27)
128606-20-2 (***pituitary adenylate cyclase-activating polypeptide*** 38)
128606-20-2 (PACAP38)

L28 ANSWER 2 OF 2 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2004:284234 BIOSIS
DN PREV200400288469
TI Passage of VIP/PACAP/secretin family across the blood-brain barrier: Therapeutic effects.
AU Dogrukol-Ak, Dilek [Reprint Author]; Tore, Fatma; Tuncel, Nese
CS Fac PharmDept Analyt Chem, Anadolu Univ, TR-26470, Eskisehir, Turkey
dak@anadolu.edu.tr
SO Current Pharmaceutical Design, (2004) Vol. 10, No. 12, pp. 1325-1340. print.

ISSN: 1381-6128 (ISSN print).
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 16 Jun 2004
Last Updated on STN: 16 Jun 2004
CC Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Pathology - Therapy 12512
Metabolism - Metabolic disorders 13020
Digestive system - Physiology and biochemistry 14004
Cardiovascular system - Physiology and biochemistry 14504
Cardiovascular system - Blood vessel pathology 14508
Endocrine - Pancreas 17008
Muscle - Pathology 17506
Nervous system - Physiology and biochemistry 20504
Nervous system - Pathology 20506
Pharmacology - General 22002
Immunology - Immunopathology, tissue immunology 34508
Medical and clinical microbiology - Virology 36006
IT Major Concepts
Biochemistry and Molecular Biophysics; Nervous System (Neural Coordination); Pharmaceuticals (Pharmacology)
IT Parts, Structures, & Systems of Organisms
blood-brain barrier: circulatory system, nervous system; brain: nervous system; central nervous system: nervous system; common carotid artery: circulatory system; gut: digestive system
IT Diseases
AIDS related neuropathy: immune system disease, nervous system disease, viral disease
IT Diseases
Alzheimer's disease: behavioral and mental disorders, nervous system disease
Alzheimer Disease (MeSH)
IT Diseases
Parkinson's disease: nervous system disease
Parkinson Disease (MeSH)
IT Diseases
amyotrophic lateral sclerosis: muscle disease, nervous system disease
Amyotrophic Lateral Sclerosis (MeSH)
IT Diseases
autism: behavioral and mental disorders
Autistic Disorder (MeSH)
IT Diseases
diabetic neuropathy: endocrine disease/pancreas, metabolic disease, nervous system disease
Diabetic Nephropathies (MeSH)
IT Diseases
nerve injury: injury, nervous system disease
IT Diseases
stroke: nervous system disease, vascular disease
***Cerebrovascular Disorders*** (MeSH)
IT Chemicals & Biochemicals
VIP/PACAP/secretin family; gastric inhibitory peptide; glucagon; glucagon like peptide-1; glucagon like peptide-2; growth hormone releasing hormone; peptide histidine methionine; peptides: lipid solubility determination; ***pituitary adenylate cyclase-activating polypeptide*** [PACAP]; secretin; ***vasoactive intestinal peptide***
IT Methods & Equipment
bolus injection: laboratory techniques; intravenous administration: laboratory techniques
IT Miscellaneous Descriptors
capillary depletion; peptide transport mechanisms; therapeutic effects

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse (common): animal model
rat (common): animal model
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 59392-49-3 (gastric inhibitory peptide)
9007-92-5 (glucagon)
89750-14-1 (glucagon like peptide-1)
89750-15-2 (glucagon like peptide-2)
9034-39-3 (growth hormone releasing hormone)
137061-48-4 (***pituitary adenylate cyclase-activating polypeptide***)
137061-48-4 (PACAP)
1393-25-5 (secretin)
37221-79-7 (***vasoactive intestinal peptide***)

=> s l24 and cerebrovascular(w)ischemia
L29 0 L24 AND CEREBROVASCULAR(W) ISCHEMIA

=> s l24 and smooth(W)bronchial(w)muscle
L30 0 L24 AND SMOOTH(W) BRONCHIAL(W) MUSCLE

=> s l24 and smooth(W)muscle
L31 135 L24 AND SMOOTH(W) MUSCLE

=> s l24 and smooth(W)muscle(w)relaxation
L32 15 L24 AND SMOOTH(W) MUSCLE(W) RELAXATION

=> d l32 1-15 abs

L32 ANSWER 1 OF 15 MEDLINE on STN
AB Penile corpus cavernosum ***smooth muscle relaxation*** can be induced by both cyclic AMP and cyclic GMP-elevating agents, but possible interactions between these two signalling pathways are still poorly understood. Using in vitro cultured rat penile corpus cavernosum smooth muscle (CCSM) cells, we have characterized the local expression and functional activities of receptors for the cAMP-elevating peptides, PACAP and VIP, and for the cGMP-elevating peptides, CNP and ANP. Stimulation of the cells with various concentrations of PACAP(-27/-38) or VIP resulted in rapid and dose-dependent increases in cyclic AMP levels. RT-PCR analyses revealed gene expression of PAC(1) and VPAC(2) but not of VPAC(1) receptors in the cells. The natriuretic peptide, CNP, and the nitric oxide donor, sodium nitroprusside, were capable of enhancing cyclic GMP formation, indicating the presence of membrane-associated in addition to soluble guanylate cyclase (sGC) activities in these cells. Findings that cyclic GMP formation was preferentially activated by CNP but not by the related peptide, ANP, were consistent with RT-PCR analyses, demonstrating gene expression of the CNP receptor, GC-B, but not of the ANP receptor, GC-A, in these cells. Prior exposure of the cells to 10(-8) M PACAP resulted in a marked down-regulation of GC-B activity, whereas sGC was not affected. These findings provide functional and molecular evidence for the presence of three receptors, PAC(1), VPAC(2) and GC-B, involved in cyclic nucleotide signalling in penile CCSM cells. The observed cross-talk of the PACAP/VIP receptors with GC-B but not with sGC may have implications for the therapy of erectile dysfunction.

L32 ANSWER 2 OF 15 MEDLINE on STN

AB Helospectin is a neuropeptide of the vasoactive intestinal polypeptide/secretin/glucagon family. Several members of this family display biological activities relevant to obstructive airway disease and although the literature in this area is rapidly expanding very little is known about the effects of helospectin. The ***smooth muscle relaxation*** induced by helospectin on human bronchi and pulmonary arteries were therefore assessed in vitro, using tissue baths. Helospectin induced a potent relaxation of human bronchi and since helospectin-like immunoreactive nerve fibers along with possible target receptors previously have been reported in the human lung, helospectin might play a role in endogenous regulation of airway tone.

L32 ANSWER 3 OF 15 MEDLINE on STN

AB The effects of pituitary adenylate cyclase-activating peptide (PACAP-38) and vasoactive intestinal polypeptide (VIP) were investigated in the gastric fundus strips of the mouse. In carbachol (CCh) precontracted strips, in the presence of guanethidine, electrical field stimulation (EFS) elicited a fast inhibitory response that may be followed, at the highest stimulation frequencies employed, by a sustained relaxation. The fast response was abolished by the nitric oxide (NO) synthesis inhibitor L-N(G)-nitro arginine (L-NNA) or by the guanylate cyclase inhibitor (ODQ), the sustained one by alpha-chymotrypsin. alpha-Chymotrypsin also increased the amplitude of the EFS-induced fast relaxation. PACAP-38 and VIP caused tetrodotoxin-insensitive sustained relaxant responses that were both abolished by alpha-chymotrypsin. Apamin did not influence relaxant responses to EFS nor relaxation to both peptides. PACAP 6-38 abolished EFS-induced sustained relaxations, increased the amplitude of the fast ones and antagonized the ***smooth muscle relaxation*** to both PACAP-38 and VIP. VIP 10-28 and [D-p-Cl-Phe6,Leu17]-VIP did not influence the amplitude of both the fast or the sustained response to EFS nor influenced the relaxation to VIP and PACAP-38. The results indicate that in strips from mouse gastric fundus peptides, other than being responsible for EFS-induced sustained relaxation, also exerts a modulatory action on the release of the neurotransmitter responsible for the fast relaxant response, that appears to be NO.

L32 ANSWER 4 OF 15 MEDLINE on STN

L32 ANSWER 5 OF 15 MEDLINE on STN

AB The relationship between vessel tone and cAMP production induced by vasoactive intestinal polypeptide (VIP), peptide histidine methionine (PHM), peptide histidine valine (PHV), ***pituitary adenylate cyclase activating polypeptide*** (PACAP-27 and PACAP-38), and neuropeptide Y (NPY) was investigated in rabbit ovarian arteries in vitro. VIP, PHM, PHV, PACAP-27, and PACAP-38 added in single-dose experiments (10(-9), 10(-8), 10(-7), and 10(-6) M) induced all a significant dose-related relaxation of noradrenaline (NA)-precontracted vessels and displayed similar potencies. VIP, PHM, PHV, PACAP-27, and PACAP-38 all increased cyclic adenosine monophosphate (cAMP) accumulation. The cAMP accumulation induced by PACAP-27 and PACAP-38 was five times higher than the cAMP content induced by the other three peptides. The peptide-induced ***smooth muscle relaxation*** did not correlate to the cAMP accumulation. NPY (10(-7) M) markedly reversed the relaxations induced by VIP, PHM, PHV, PACAP-27, and PACAP-38, but did not influence the cAMP production induced by these peptides. In conclusion, the relaxation induced by VIP, PHM, PHV, PACAP-27, and PACAP-38 and the contraction induced by NPY are not solely related to the changes of cAMP contents. These findings indicate that in addition to cAMP, another intracellular signal transduction pathway may be involved in the relaxation and contraction induced by these peptides in rabbit ovarian artery.

L32 ANSWER 6 OF 15 MEDLINE on STN

AB Hirschsprung's disease (HSCR) is characterized by a non-propulsive distal intestinal segment (usually colon) leading to a functional obstruction. An absence of ganglia in the affected segment explains the synonymous term "aganglionosis coli". The lack of peristalsis is partly due to a deficient intestinal ***smooth muscle relaxation*** based on an absence of non-adrenergic, non-cholinergic (NANC) inhibitory innervation. Morphological studies using conventional microscopy, immunohistochemistry and immunochemistry against general neuronal markers and neuropeptides have been used to characterize the disturbed NANC innervation in HSCR. An increased cholinergic and adrenergic innervation is registered in the aganglionic segment in spite of the lack of neuronal cell bodies: Neuropeptides like ***vasoactive intestinal peptide*** (VIP), ***pituitary adenylate cyclase-activating polypeptide*** (PACAP), gastrin-releasing peptide (GRP), calcitonin gene-related peptide (CGRP), substance P (SP), enkephalins and galanin immunoreactive nerve fibres are all reduced in number in the aganglionic segment. In contrast, neuropeptide Y (NPY)-containing nerve fibres are increased in number in the diseased segment, probably reflecting the adrenergic hyperinnervation. General neuronal markers including chromogranins have been used to map the neuronal network in the HSCR intestine and also to investigate the endocrine cell system in the intestinal mucosa. Nitric oxide is a potent component of the NANC inhibitory innervation and its synthesizing enzyme, nitric oxide synthase (NOS), is shown to be almost absent in the neuronal system in aganglionic intestine.

L32 ANSWER 7 OF 15 MEDLINE on STN

AB To elucidate the effects of ***vasoactive intestinal peptide*** (VIP) and pituitary adenylate cyclase activating peptide (PACAP) on airway smooth muscle function, we studied rabbit isolated tracheal segments under isometric conditions in vitro. Addition of VIP and PACAP dose-dependently relaxed tracheal smooth muscle precontracted with acetylcholine, with the order potency being PACAP (1) > or = VIP (0.78), accompanied by the corresponding increase in intracellular cyclic AMP levels. The VIP- and PACAP-induced muscle relaxations were significantly inhibited by ouabain and K(+)-free medium. Incubation of tissues with VIP reduced the contractile responses to electrical field stimulation, whereas PACAP had no effect. These results suggest that VIP and PACAP may cause bronchodilation through activation of Na(+)-K(+)-ATPase and that VIP but not PACAP inhibits the release of acetylcholine from the cholinergic nerve terminals.

L32 ANSWER 8 OF 15 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

AB Penile corpus cavernosum ***smooth muscle relaxation*** can be induced by both cyclic AMP and cyclic GMP-elevating agents, but possible interactions between these two signalling pathways are still poorly understood. Using in vitro cultured rat penile corpus cavernosum smooth muscle (CCSM) cells, we have characterized the local expression and functional activities of receptors for the cAMP-elevating peptides, PACAP and VIP, and for the cGMP-elevating peptides, CNP and ANP. Stimulation of the cells with various concentrations of PACAP-27/-38 or VIP resulted in rapid and dose-dependent increases in cyclic AMP levels. RT-PCR analyses revealed gene expression of PAC1 and VPAC2 but not of VPAC1 receptors in the cells. The natriuretic peptide, CNP, and the nitric oxide donor, sodium nitroprusside, were capable of enhancing cyclic GMP formation, indicating the presence of membrane-associated in addition to soluble guanylate cyclase (sGC) activities in these cells. Findings that cyclic GMP formation was preferentially activated by CNP but not by the related peptide, ANP, were consistent with RT-PCR analyses, demonstrating gene expression of the CNP receptor, GC-B, but not of the ANP receptor, GC-A, in these cells. Prior exposure of the cells to 10-8 M PACAP resulted in a marked down-regulation of GC-B activity, whereas sGC was not affected. These findings provide functional and molecular evidence for the presence

of three receptors, PAC1, VPAC2 and GC-B, involved in cyclic nucleotide signalling in penile CCSM cells. The observed cross-talk of the PACAP/VIP receptors with GC-B but not with sGC may have implications for the therapy of erectile dysfunction.

L32 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
AB As ***pituitary adenylate cyclase-activating polypeptide*** 38 (PACAP 38)- and ***vasoactive intestinal peptide*** (VIP) are widely distributed in the urinary tract, the current study investigated the receptors and mechanisms involved in relaxations induced by these peptides in the pig bladder neck. Urothelium-denuded strips were suspended in organ baths for isometric force recordings and the relaxations to VIP and PACAP analogs were investigated. Key results showed that VIP, PACAP 38, PACAP 27 and [Ala11,22,28]-VIP produced similar relaxations. Inhibition of neuronal voltage-gated Ca2+ channels reduced relaxations to PACAP 38 and increased those induced by VIP. Blockade of capsaicin-sensitive primary afferents (CSPA), nitric oxide (NO)-synthase or guanylate cyclase reduced the PACAP 38 relaxations but failed to modify the VIP responses. Inhibition of VIP/PACAP receptors and of voltage-gated K+ channels reduced PACAP 38 and VIP relaxations, which were not modified by the K+ channel blockers iberiotoxin, charybdotoxin, apamin or glibenclamide. The phosphodiesterase 4 inhibitor rolipram and the adenylate cyclase activator forskolin produced potent relaxations. Blockade of protein kinase A (PKA) reduced PACAP 38- and VIP-induced relaxations. Thus, PACAP 38 and VIP relax the pig urinary bladder neck through muscle VPAC2 receptors linked to the cAMP-PKA pathway and involve activation of voltage-gated K+ channels. Facilitatory PAC1 receptors located at CSPA and coupled to NO release, and inhibitory VPAC receptors at motor endings are also involved in the relaxations to PACAP 38 and VIP, resp. VIP/PACAP receptor antagonists could be useful in the therapy of urinary incontinence produced by intrinsic sphincter deficiency.

L32 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
AB The authors investigated the contribution of pituitary adenylate cyclase activating peptide (PACAP) to inhibitory nonadrenergic noncholinergic (inhibitory-NANC) relaxation of tracheal smooth muscle in cats. The authors also investigated the roles of ***vasoactive intestinal peptide*** (VIP) and nitric oxide (NO) on this function. Smooth muscle strips prepared from feline trachea were precontracted with 1 μM serotonin, and inhibitory-NANC relaxation was induced by elec.-field stimulation in the presence of atropine and propranolol. PACAP-(6-38) (a selective antagonist of PACAP; 1, 3 and 10 μM), VIP-(10-28) (a selective antagonist of VIP; 1, 3 and 10 μM) and Nω-nitro-l-arginine Me ester (L-NAME, a selective NO synthase inhibitor; 3, 10 and 30 μM) each partially but significantly attenuated the amplitude of inhibitory-NANC relaxation. The effects of PACAP-(6-38) and VIP-(10-28) were additive. Addition of PACAP-(6-38) and/or VIP-(10-28) further attenuated relaxation in the presence of L-NAME. These results suggest that PACAP, VIP and NO contribute to the relaxation induced by inhibitory-NANC in tracheal smooth muscle in cats, and that they mediate this relaxation via different pathways.

L32 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2007 ACS on STN
AB ***Pituitary adenylate cyclase-activating polypeptide*** (PACAP) is a new member of the secretin/glucagon peptides family, being most homologous to ***vasoactive intestinal peptide*** (VIP). Possible effects of PACAP on the rat gastrointestinal smooth muscle in vitro were investigated. PACAP reduced basal smooth-muscle contractions in all portions of the gastrointestinal tract, whereas the effect of VIP was region-specific. The inhibitory effect of PACAP in mid-colon was approx. 100-fold greater than that of VIP. PACAP significantly inhibited smooth-muscle contractions induced by acetylcholine or carbachol. The

inhibitory effect of PACAP was not affected by hexamethonium and was additive to the inhibitory effect of atropine and pirenzepine. PACAP inhibited smooth-muscle contractions induced by substance P, cholecystokinin, and galanin, even after atropine treatment. Although the exact mechanism of the inhibitory action of PACAP remains to be clarified, PACAP appears to exert its effect in the rat at a site other than muscarinic receptors, probably through a direct effect on gastrointestinal smooth muscle.

L32 ANSWER 12 OF 15 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

AB Aims: To investigate the role played by ***pituitary adenylate cyclase activating polypeptide*** 38 (PACAP 38) in the non-adrenergic non-cholinergic (NANC) neurotransmission of the pig urinary bladder neck. Methods: Urothelium-denuded bladder neck strips were dissected and mounted in organ baths containing a physiological saline solution (PSS) at 37°C and gassed with 5% CO(2) and 95% O(2), for isometric force recording. The relaxations to transmural nerve stimulation (EFS) or PACAP 38 were performed on strips precontracted with 1 μM phenylephrine (PhE). EFS experiments were carried out in the absence and the presence of guanethidine (10 μM), atropine (0.1 μM), and N(G)-nitro-L-arginine (L-NOARG, 100 μM), to block noradrenergic neurotransmission, muscarinic receptors, and nitric oxide (NO) synthase, respectively. Results: EFS (2-16 Hz, 1 ms duration, 20 sec trains, 75 mA current output) evoked frequency-dependent relaxations which were reduced by the VIP/PACAP receptor antagonist PACAP (6-38) (3 μM), and by the neurotoxin of the capsaicin-sensitive primary afferents capsaicin (10 μM), and abolished by the neuronal voltage-activated Na channel blocker tetrodotoxin (TTX, 1 μM). The ***vasoactive intestinal peptide*** (VIP) receptor antagonist [Lys (1) , Pro(2,5), Arg(3,4), Tyr(6)]-VIP (3 μM) failed to modify the EFS-induced relaxations. PACAP 38 (1 nM-1 μM) induced concentration-dependent relaxations which were reduced by PACAP (6-38), TTX and by the neuronal voltage-gated Ca(2+) channel inhibitor Ca (2+) ω-conotoxin GVIA (ω-CgTX, 1 μM).
Conclusions: The results suggest that PACAP 38, mainly released from capsaicin-sensitive primary afferents, is involved in the NANC inhibitory neurotransmission of the pig urinary bladder heck, producing relaxation through neuronal and muscle VIP/PACAP receptor activation. .COPYRGT. 2006 Wiley-Liss, Inc.

L32 ANSWER 13 OF 15 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

AB 1. The mechanisms and receptors involved in the ***vasoactive intestinal peptide*** (VIP)- and ***pituitary adenylate cyclase-activating polypeptide*** (PACAP)-induced relaxations of the pig intravesical ureter were investigated. 2. VIP, PACAP 38 and PACAP 27 concentration-dependently relaxed U46619-contracted ureteral strips with a similar potency. [Ala(11,22,28)]-VIP, a VPAC(1) agonist, showed inconsistent relaxations. 3. The neuronal voltage-gated Ca(2+) channel inhibitor, ω-conotoxin GVIA (ω-CgTX, 1 μM), reduced the VIP relaxations. Urothelium removal or blockade of capsaicin-sensitive primary afferents, nitric oxide (NO) synthase and guanylate cyclase with capsaicin (10 μM), N(G)-nitro-L-arginine (L-NOARG, 100 μM) and 1H-[1,2,4]-oxadiazolo[4,3-a]quinoxalin-1-one (ODQ, 5 μM), respectively, did not change the VIP relaxations. However, the PACAP 38 relaxations were reduced by μ-CgTX, capsaicin, L-NOARG and ODQ. 4. The VIP and VIP/PACAP receptor antagonists, [Lys(1), Pro(2,5), Arg(3,4), Tyr(6)]-VIP (1 μM) and PACAP (6-38) (0.4 μM), inhibited VIP and VIP and PACAP 38, respectively, relaxations. 5. The nonselective and large-conductance Ca(2)-activated K(+) channel blockers, tetraethylammonium (3 mM) and charybdotoxin (0.1 μM), respectively, and neuropeptide Y (0.1 μM) did not modify the VIP relaxations. The small-conductance Ca(2)-activated

K(+) channel blocker apamin (1 μM) did not change the PACAP 27 relaxations. 6. The cAMP-dependent protein kinase A (PKA) blocker, 8-(4-chlorophenylthio)adenosine-3', 5'-cyclic monophosphorothioate (Rp-8-CPT-cAMPS, 100 'M), reduced VIP relaxations. The phosphodiesterase 4 inhibitor rolipram and the adenylate cyclase activator forskolin relaxed ureteral preparations. The rolipram relaxations were reduced by Rp-8-CPT-cAMPS. Forskolin (30 nM) evoked a potentiation of VIP relaxations. 7. These results suggest that VIP and PACAP relax the pig ureter through smooth muscle receptors, probably of the VPAC (2) subtype, linked to a cAMP-PKA pathway. Neuronal VPAC receptors localized at motor nerves and PAC(1) receptors placed at sensory nerves and coupled to NO release, seem also to be involved in the VIP and PACAP 38 relaxations.

L32 ANSWER 14 OF 15 EMBASE 

AB Hirschsprung's disease (HSCR) is characterized by a non-propulsive distal intestinal segment (usually colon) leading to a functional obstruction. An absence of ganglia in the affected segment explains the synonymous term <<aganglionosis coli>>. The lack of peristalsis is partly due to a deficient intestinal ***smooth muscle relaxation*** based on an absence of non-adrenergic, non-cholinergic (NANC) inhibitory innervation. Morphological studies using conventional microscopy, immunohistochemistry and immunochemistry against general neuronal markers and neuropeptides have been used to characterize the disturbed NANC innervation in HSCR. An increased cholinergic and adrenergic innervation is registered in the aganglionic segment in spite of the lack of neuronal cell bodies: Neuropeptides like ***vasoactive intestinal peptide*** (VIP), ***pituitary adenylate cyclase-activating polypeptide*** (PACAP), gastrin releasing peptide (GRP), calcitonin generelated peptide (CGRP), substance P (SP), enkephalins and galanin immunoreactive nerve fibres are all reduced in number in the aganglionic segment. In contrast, neuropeptide Y (NPY)-containing nerve fibres are increased in number in the diseased segment, probably reflecting the adrenergic hyperinnervation. General neuronal markers including chromogranins have been used to map the neuronal network in the HSCR intestine and also to investigate the endocrine cell system in the intestinal mucosa. Nitric oxide is a potent component of the NANC inhibitory innervation and its synthesizing enzyme, nitric oxide synthase (NOS), is shown to be almost absent in the neuronal system in aganglionic intestine.

L32 ANSWER 15 OF 15 EMBASE 

AB ***Pituitary adenylate cyclase-activating polypeptide*** (PACAP) is a new member of the secretin/glucagon peptides family, being most homologous to ***vasoactive intestinal peptide*** (VIP). The present study was designed to investigate a possible effect of PACAP on the rat gastrointestinal smooth muscle in vitro. We demonstrated that 1) PACAP reduced basal smooth-muscle contractions in all portions of the gastrointestinal tract, but the effect of VIP was region-specific. The inhibitory effect of PACAP in mid-colon was approximately 100 times greater than that of VIP. 2) PACAP significantly inhibited smooth-muscle contractions induced by acetylcholine or carbachol. The inhibitory effect of PACAP was not affected by hexamethonium and was additive to the inhibitory effect of atropine and pirenzepine. 3) PACAP inhibited smooth-muscle contractions induced by substance P, cholecystokinin, and galanin, even after atropine treatment. Although the exact mechanism of the inhibitory action of PACAP remains to be clarified, PACAP appears to exert its effect in the rat at a site other than muscarinic receptors, probably through a direct effect on gastrointestinal smooth muscle in vitro.

=> d l32 2-3, 5-6, 14 all

L32 ANSWER 2 OF 15 MEDLINE on STN
AN 2001469808 MEDLINE
DN PubMed ID: 11514015
TI Helospectin, induces a potent relaxation of human airways in vitro.
AU Cardell M; Cardell L O
CS Department of Obstetrics and Gynaecology, Lund University Hospital, Lund, Sweden.
SO Peptides, (2001 Sep) Vol. 22, No. 9, pp. 1359-62.
Journal code: 8008690. ISSN: 0196-9781.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200112
ED Entered STN: 30 Aug 2001
Last Updated on STN: 22 Jan 2002
Entered Medline: 21 Dec 2001
AB Helospectin is a neuropeptide of the vasoactive intestinal polypeptide/secretin/glucagon family. Several members of this family display biological activities relevant to obstructive airway disease and although the literature in this area is rapidly expanding very little is known about the effects of helospectin. The ***smooth muscle relaxation*** induced by helospectin on human bronchi and pulmonary arteries were therefore assessed in vitro, using tissue baths. Helospectin induced a potent relaxation of human bronchi and since helospectin-like immunoreactive nerve fibers along with possible target receptors previously have been reported in the human lung, helospectin might play a role in endogenous regulation of airway tone.
CT Acetylcholine: PD, pharmacology
Aged
*Bronchi: DE, drug effects
Bronchi: ME, metabolism
Bronchodilator Agents: PD, pharmacology
Comparative Study
Dose-Response Relationship, Drug
Humans
In Vitro
Lung: BS, blood supply
Lung: CH, chemistry
Middle Aged
*Neuropeptides: PD, pharmacology
*Peptides: PD, pharmacology
***Pituitary Adenylate Cyclase-Activating Polypeptide***
*Pulmonary Artery: DE, drug effects
Pulmonary Artery: ME, metabolism
Research Support, Non-U.S. Gov't
***Vasoactive Intestinal Peptide: PD, pharmacology***
*Vasodilation: DE, drug effects
RN 141443-72-3 (helospectin); ***37221-79-7 (Vasoactive Intestinal Peptide)***; 51-84-3 (Acetylcholine)
CN 0 (ADCYAP1 protein, human); 0 (Bronchodilator Agents); 0 (Neuropeptides); 0 (Peptides); 0 (***Pituitary Adenylate Cyclase -Activating Polypeptide***)

L32 ANSWER 3 OF 15 MEDLINE on STN
AN 2001408561 MEDLINE
DN PubMed ID: 11179775
TI Modulation of nitrergic relaxant responses by peptides in the mouse gastric fundus.
AU Baccari M C; Calamai F
CS Department of Physiology, University of Florence, Viale G.B. Morgagni 63, 50134, Florence, Italy.. mcaterina.baccari@unifi.it

SO Regulatory peptides, (2001 Apr 2) Vol. 98, No. 1-2, pp. 27-32.
Journal code: 8100479. ISSN: 0167-0115.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200107
ED Entered STN: 23 Jul 2001
Last Updated on STN: 23 Jul 2001
Entered Medline: 19 Jul 2001
AB The effects of pituitary adenylate cyclase-activating peptide (PACAP-38) and vasoactive intestinal polypeptide (VIP) were investigated in the gastric fundus strips of the mouse. In carbachol (CCh) precontracted strips, in the presence of guanethidine, electrical field stimulation (EFS) elicited a fast inhibitory response that may be followed, at the highest stimulation frequencies employed, by a sustained relaxation. The fast response was abolished by the nitric oxide (NO) synthesis inhibitor L-N(G)-nitro arginine (L-NNA) or by the guanylate cyclase inhibitor (ODQ), the sustained one by alpha-chymotrypsin. alpha-Chymotrypsin also increased the amplitude of the EFS-induced fast relaxation. PACAP-38 and VIP caused tetrodotoxin-insensitive sustained relaxant responses that were both abolished by alpha-chymotrypsin. Apamin did not influence relaxant responses to EFS nor relaxation to both peptides. PACAP 6-38 abolished EFS-induced sustained relaxations, increased the amplitude of the fast ones and antagonized the ***smooth muscle relaxation*** to both PACAP-38 and VIP. VIP 10-28 and [D-p-Cl-Phe6,Leu17]-VIP did not influence the amplitude of both the fast or the sustained response to EFS nor influenced the relaxation to VIP and PACAP-38. The results indicate that in strips from mouse gastric fundus peptides, other than being responsible for EFS-induced sustained relaxation, also exerts a modulatory action on the release of the neurotransmitter responsible for the fast relaxant response, that appears to be NO.
CT Check Tags: Male
Animals
Apamin: PD, pharmacology
Carbachol: PD, pharmacology
Cholinergic Agonists: PD, pharmacology
Chymotrypsin: PD, pharmacology
Electric Stimulation
Enzyme Inhibitors: PD, pharmacology
Gastric Fundus: DE, drug effects
*Gastric Fundus: PH, physiology
Guanylate Cyclase: AI, antagonists & inhibitors
In Vitro
Mice
Mice, Inbred C57BL
Muscle Contraction: DE, drug effects
*Muscle Relaxation: DE, drug effects
Neuropeptides: AI, antagonists & inhibitors
Neuropeptides: ME, metabolism
*Neuropeptides: PD, pharmacology
Neurotransmitter Agents: ME, metabolism
*Neurotransmitter Agents: PD, pharmacology
Nitroarginine: PD, pharmacology
Oxadiazoles: PD, pharmacology
Peptide Fragments: PD, pharmacology
***Pituitary Adenylate Cyclase-Activating Polypeptide***
Quinoxalines: PD, pharmacology
Research Support, Non-U.S. Gov't
***Vasoactive Intestinal Peptide: AI, antagonists & inhibitors***
***Vasoactive Intestinal Peptide: ME, metabolism***
****Vasoactive Intestinal Peptide: PD, pharmacology***
RN 2149-70-4 (Nitroarginine); 24345-16-2 (Apamin); ***37221-79-7***

***(Vasoactive Intestinal Peptide)***; 51-83-2 (Carbachol); ***69856-17-3 (vasoactive intestinal peptide (10-28))***

CN 0 (1H-(1,2,4)oxadiazolo(4,3-a)quinoxalin-1-one); 0 (Adcyap1 protein, mouse); 0 (Cholinergic Agonists); 0 (Enzyme Inhibitors); 0 (Neuropeptides); 0 (Neurotransmitter Agents); 0 (Oxadiazoles); 0 (Peptide Fragments); 0 (***Pituitary Adenylate Cyclase-Activating Polypeptide***); 0 (Quinoxalines); 0 (pituitary adenylate-cyclase-activating-peptide (6-38)); EC 3.4.21.- (chymotrypsin A); EC 3.4.21.1 (Chymotrypsin); EC 4.6.1.2 (Guanylate Cyclase)

L32 ANSWER 5 OF 15 MEDLINE on STN
AN 97001779 MEDLINE
DN PubMed ID: 8844771
TI Vascular effects and cyclic AMP production produced by VIP, PHM, PHV, PACAP-27, PACAP-38, and NPY on rabbit ovarian artery.
AU Yao W; Sheikh S P; Ottesen B; Jorgensen J C
CS Department of Obstetrics and Gynecology, Hvidovre Hospital, University of Copenhagen, Denmark.
SO Peptides, (1996) Vol. 17, No. 5, pp. 809-15.
Journal code: 8008690. ISSN: 0196-9781.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199702
ED Entered STN: 5 Mar 1997
Last Updated on STN: 5 Mar 1997
Entered Medline: 19 Feb 1997
AB The relationship between vessel tone and cAMP production induced by vasoactive intestinal polypeptide (VIP), peptide histidine methionine (PHM), peptide histidine valine (PHV), ***pituitary adenylate cyclase activating polypeptide*** (PACAP-27 and PACAP-38), and neuropeptide Y (NPY) was investigated in rabbit ovarian arteries in vitro. VIP, PHM, PHV, PACAP-27, and PACAP-38 added in single-dose experiments (10(-9), 10(-8), 10(-7), and 10(-6) M) induced all a significant dose-related relaxation of noradrenaline (NA)-precontracted vessels and displayed similar potencies. VIP, PHM, PHV, PACAP-27, and PACAP-38 all increased cyclic adenosine monophosphate (cAMP) accumulation. The cAMP accumulation induced by PACAP-27 and PACAP-38 was five times higher than the cAMP content induced by the other three peptides. The peptide-induced ***smooth muscle relaxation*** did not correlate to the cAMP accumulation. NPY (10(-7) M) markedly reversed the relaxations induced by VIP, PHM, PHV, PACAP-27, and PACAP-38, but did not influence the cAMP production induced by these peptides. In conclusion, the relaxation induced by VIP, PHM, PHV, PACAP-27, and PACAP-38 and the contraction induced by NPY are not solely related to the changes of cAMP contents. These findings indicate that in addition to cAMP, another intracellular signal transduction pathway may be involved in the relaxation and contraction induced by these peptides in rabbit ovarian artery.
CT Check Tags: Female
Animals
Arteries: DE, drug effects
Arteries: PH, physiology
Comparative Study
*Cyclic AMP: BI, biosynthesis
Dose-Response Relationship, Drug
Neuropeptide Y: AD, administration & dosage
Neuropeptide Y: PD, pharmacology
Neuropeptides: AD, administration & dosage
*Neuropeptides: PD, pharmacology
Neurotransmitter Agents: AD, administration & dosage
Neurotransmitter Agents: PD, pharmacology
Ovary: BS, blood supply

Peptide Fragments: AD, administration & dosage
Peptide Fragments: PD, pharmacology
Peptide PHI: AD, administration & dosage
Peptide PHI: PD, pharmacology
***Pituitary Adenylate Cyclase-Activating Polypeptide***
Protein Precursors: AD, administration & dosage
Protein Precursors: PD, pharmacology
Rabbits
Research Support, Non-U.S. Gov't
***Vasoactive Intestinal Peptide: AD, administration & dosage***
***Vasoactive Intestinal Peptide: PD, pharmacology***
*Vasoconstriction: DE, drug effects
*Vasodilation: DE, drug effects
RN 111366-38-2 (peptide histidine valine 42); ***37221-79-7 (Vasoactive Intestinal Peptide)***; 60-92-4 (Cyclic AMP)
CN 0 (Neuropeptide Y); 0 (Neuropeptides); 0 (Neurotransmitter Agents); 0 (Peptide Fragments); 0 (Peptide PHI); 0 (***Pituitary Adenylate Cyclase-Activating Polypeptide***); 0 (Protein Precursors)

L32 ANSWER 6 OF 15 MEDLINE on STN
AN 95072370 MEDLINE
DN PubMed ID: 7981507
TI Hirschsprung's disease--immunohistochemical findings.
AU Larsson L T
CS Department of Pediatric Surgery, University of Lund, Sweden.
SO Histology and histopathology, (1994 Jul) Vol. 9, No. 3, pp. 615-29. Ref: 100
Journal code: 8609357. ISSN: 0213-3911.
CY Spain
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 199501
ED Entered STN: 16 Jan 1995
Last Updated on STN: 16 Jan 1995
Entered Medline: 3 Jan 1995
AB Hirschsprung's disease (HSCR) is characterized by a non-propulsive distal intestinal segment (usually colon) leading to a functional obstruction. An absence of ganglia in the affected segment explains the synonymous term "aganglionosis coli". The lack of peristalsis is partly due to a deficient intestinal ***smooth muscle relaxation*** based on an absence of non-adrenergic, non-cholinergic (NANC) inhibitory innervation. Morphological studies using conventional microscopy, immunohistochemistry and immunochemistry against general neuronal markers and neuropeptides have been used to characterize the disturbed NANC innervation in HSCR. An increased cholinergic and adrenergic innervation is registered in the aganglionic segment in spite of the lack of neuronal cell bodies: Neuropeptides like ***vasoactive intestinal peptide*** (VIP), ***pituitary adenylate cyclase-activating polypeptide*** (PACAP), gastrin-releasing peptide (GRP), calcitonin gene-related peptide (CGRP), substance P (SP), enkephalins and galanin immunoreactive nerve fibres are all reduced in number in the aganglionic segment. In contrast, neuropeptide Y (NPY)-containing nerve fibres are increased in number in the diseased segment, probably reflecting the adrenergic hyperinnervation. General neuronal markers including chromogranins have been used to map the neuronal network in the HSCR intestine and also to investigate the endocrine cell system in the intestinal mucosa. Nitric oxide is a potent component of the NANC inhibitory innervation and its synthesizing enzyme, nitric oxide synthase (NOS), is shown to be almost absent in the neuronal system in aganglionic intestine.
CT Biological Markers

Colon: IR, innervation
*Colon: ME, metabolism
*Hirschsprung Disease: ME, metabolism
Immunohistochemistry
Nerve Tissue: PA, pathology
*Neuropeptides: IP, isolation & purification
*Neurotransmitter Agents: IP, isolation & purification
CN 0 (Biological Markers); 0 (Neuropeptides); 0 (Neurotransmitter Agents)

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AN 94235815 EMBASE
DN 1994235815
TI Hirschsprung's disease - Immunohistochemical findings.
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CS Department of Pediatric Surgery, University Hospital,S-221 85 Lund, Sweden
SO Histology and Histopathology, (1994) Vol. 9, No. 3, pp. 615-629. .
ISSN: 0213-3911 CODEN: HIHIES
CY Spain
DT Journal; General Review
FS 005 General Pathology and Pathological Anatomy
048 Gastroenterology
LA English
SL English
ED Entered STN: 26 Aug 1994
Last Updated on STN: 26 Aug 1994
AB Hirschsprung's disease (HSCR) is characterized by a non-propulsive distal intestinal segment (usually colon) leading to a functional obstruction. An absence of ganglia in the affected segment explains the synonymous term <<aganglionosis coli>>. The lack of peristalsis is partly due to a deficient intestinal ***smooth muscle relaxation*** based on an absence of non-adrenergic, non-cholinergic (NANC) inhibitory innervation. Morphological studies using conventional microscopy, immunohistochemistry and immunochemistry against general neuronal markers and neuropeptides have been used to characterize the disturbed NANC innervation in HSCR. An increased cholinergic and adrenergic innervation is registered in the aganglionic segment in spite of the lack of neuronal cell bodies: Neuropeptides like ***vasoactive intestinal peptide*** (VIP), ***pituitary adenylate cyclase-activating polypeptide*** (PACAP), gastrin releasing peptide (GRP), calcitonin generelated peptide (CGRP), substance P (SP), enkephalins and galanin immunoreactive nerve fibres are all reduced in number in the aganglionic segment. In contrast, neuropeptide Y (NPY)-containing nerve fibres are increased in number in the diseased segment, probably reflecting the adrenergic hyperinnervation. General neuronal markers including chromogranins have been used to map the neuronal network in the HSCR intestine and also to investigate the endocrine cell system in the intestinal mucosa. Nitric oxide is a potent component of the NANC inhibitory innervation and its synthesizing enzyme, nitric oxide synthase (NOS), is shown to be almost absent in the neuronal system in aganglionic intestine.
CT Medical Descriptors:
*hirschsprung disease: DI, diagnosis
*hirschsprung disease: ET, etiology
human
immunochemistry
immunohistochemistry
immunoreactivity
intestine innervation
neurotransmission
review
***smooth muscle relaxation***
Drug Descriptors:
*enkephalin: EC, endogenous compound

*galanin: EC, endogenous compound
*gastrin releasing peptide: EC, endogenous compound
*hypophysis adenylate cyclase activating polypeptide: EC, endogenous compound
*neuropeptide: EC, endogenous compound
*neuropeptide y: EC, endogenous compound
*substance p: EC, endogenous compound
*vasoactive intestinal polypeptide: EC, endogenous compound
chromogranin

RN (galanin) 88813-36-9; (gastrin releasing peptide) 74815-57-9, 80043-53-4; (hypophysis adenylate cyclase activating polypeptide) 137061-48-4; (neuropeptide y) 82785-45-3, 83589-17-7; (substance p) 33507-63-0; (vasoactive intestinal polypeptide) 37221-79-7